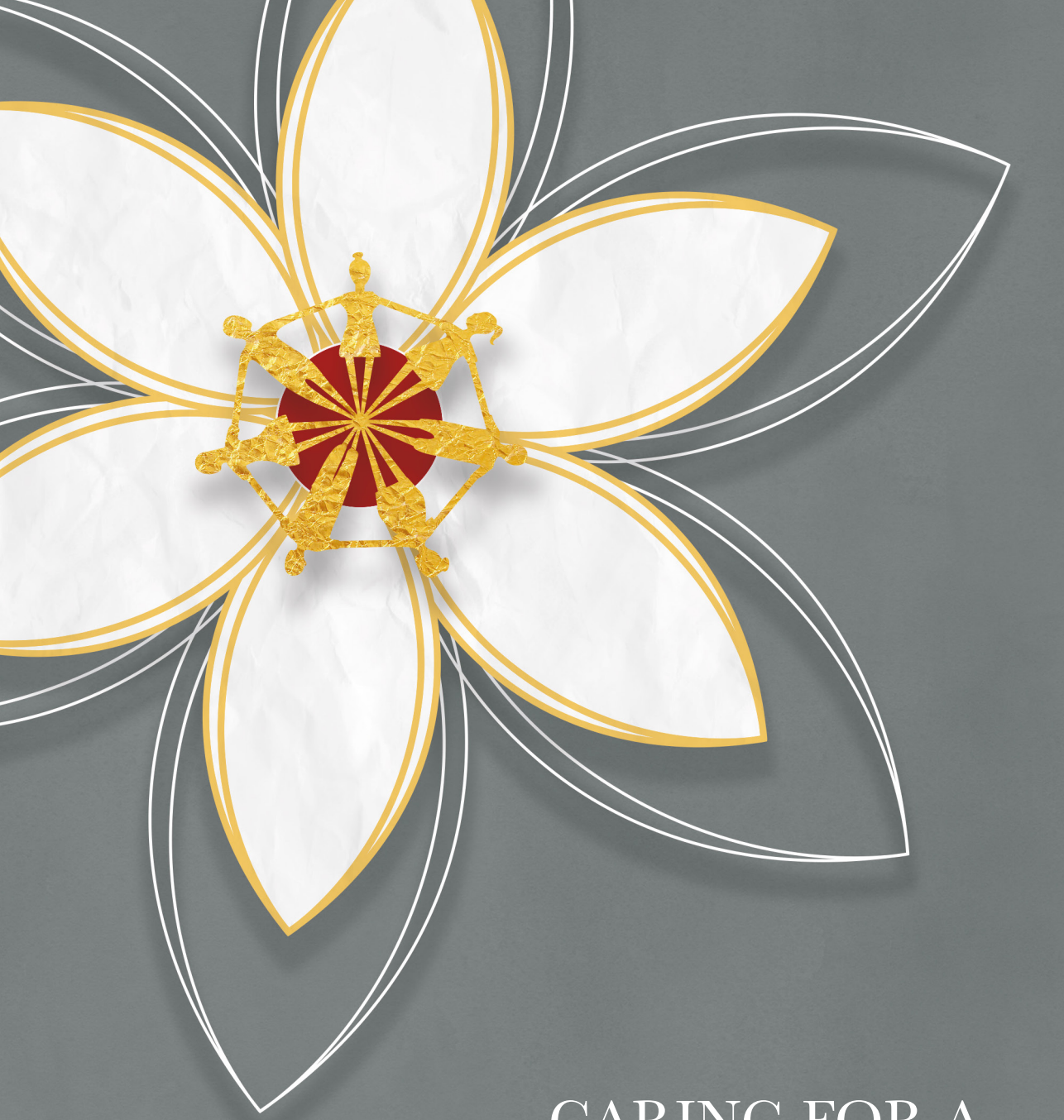


CARING FOR A PATIENT WITH CANCER

The psychosocial impact on informal caregivers

Simône Langenberg

CARING FOR A PATIENT WITH CANCER

The psychosocial impact on informal caregivers

Simône Langenberg

The work presented in this thesis was carried out within the Radboud Institute for Health Sciences at the Department of Medical Oncology of the Radboud university medical center, Nijmegen, the Netherlands.

ISBN: 978-94-6416-115-1

Cover design and layout: © evelienjagtman.com
Printed by: Ridderprint BV

CARING FOR A PATIENT WITH CANCER

The psychosocial impact on informal caregivers

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen
op donderdag 30 september 2021
om 12:30 uur precies

door

Simone Marie Claire Hélène Langenberg

geboren op 30 september 1984
te Loosdrecht

Promotoren:
Prof. dr. W.T.A. van der Graaf
Prof. dr. J.B. Prins
Prof. dr. C.M.L. van Herpen

Copromotor:
Dr. A.N.M. Wymenga (Medisch Spectrum Twente)

Manuscriptcommissie:
Prof. dr. A.E.M. Speckens (voorzitter)
Prof. dr. N.M.A. Blijlevens
Prof. dr. C.C.D van der Rijt (Erasmus MC)

"**What is the bravest thing you've ever said**?" asked the boy
"**Help.**" said the horse

Charlie Mackesy

TABLE OF CONTENTS

Chapter 1

General introduction

GENERAL INTRODUCTION

In 2018, 18 million people were diagnosed with cancer and 9.6 million people died as a consequence of the disease worldwide [1]. In this same year, 116,537 inhabitants of the Netherlands were diagnosed with cancer and 45,206 patients died as a consequence of cancer [2]. There are several treatments for cancer, applied separately or in combination: surgery, radiotherapy and/or systemic treatment. Systemic therapy can be chemotherapy, targeted therapy, immunotherapy and/or hormonal treatment. Regarding systemic treatment, we distinguish three phases when this therapy is applied with curative intent: 1) neo-adjuvant (prior to surgery), 2) concomitant (together with radiotherapy) and 3) adjuvant (after surgery and/or radiotherapy). When curative treatment is not possible, systemic treatment is also applied in the palliative phase. During treatment, a patient faces many challenges, which makes good support indispensable. Most of the time, this care is provided by informal caregivers.

Informal caregivers and their challenges

An **informal caregiver** provides unpaid and often long-term care for a family member or friend in need. In the Netherlands, 4.4 million individuals (25%) provide care to a significant other [3]. Of these 750,000 provide long-term care (> 3 months and/or > 8 hours every week) [3]. Of the informal caregivers who provide long-term care, it is not clear how they are distributed between caring for patients with dementia, cancer or other morbidities. The informal caregiver is often a spouse, parent, child or sibling, but can also be a friend or neighbour. Furthermore, for paediatric cancer patients and Adolescent and Young Adults (AYA's), the parent(s) can be their informal caregiver(s). Informal caregivers support patients in many ways. They provide practical support (transportation, accompany a patient to the hospital, both planned (for treatment) or unplanned (for treating complications), do administration tasks, arrange practical instruments at home, support with activities of daily living, managing the household, as well as emotional support dealing with the patients' disease. Supporting a patient emotionally is an often difficult though important aspect. Furthermore, informal caregivers play an important role in helping the patient navigate and decide what treatment option suits them best. This challenges informal caregivers, as they also have their personal life and responsibilities [4]. This can lead to burden, psychological distress (hereafter described as "distress") and depression in informal caregivers when a patient is treated for cancer [4]. When a patient survives after cancer treatment, fear of patients' cancer recurrence might be a problem for informal caregivers as well [5]. When a patients dies as a consequence of cancer, depression is seen and may

coincide with complicated grief [6]. Both informal caregivers' mental health and their physical health can be affected. Before describing the studies performed in this thesis, more background information about burden, distress, depression, complicated grief, health-related quality of life, fatigue, and fear of recurrence will be given.

Burden

Experiencing **burden** is different for every informal caregiver as a consequence of the multidimensional aspect of providing support to a significant other [7,4]. Informal caregiver burden has adverse effects on their general health and other roles they fulfil in life [4,7]. When burden is experienced as a problem, there is an imbalance between informal caregivers' resilience, resources and personal capacities and patients' care demands. Risk factors for higher levels of informal caregivers' burden are divers and range from demographic factors (being female, living together with the care recipient), psychological factors (depression, fewer coping strategies, distress), social factors (social isolation), financial factors (discontinuation of own employment, financial stress) to care-related factors (spending more hours caring, lack of choice becoming a caregiver) [4]. In the Netherlands, overall, 380,000 informal caregivers are heavily burdened [3]. Although this number of burdened informal caregivers is not specific for informal caregivers of patients with cancer, it delineates that there is a vulnerable group of informal caregivers that might need extra support.

Distress, depression and complicated grief

Distress, defined by the National Cancer Institute as 'emotional, social, spiritual, physical pain or suffering that may cause a person to feel sad, afraid, depressed, anxious or lonely', is an important psychological morbidity, which often coincides with burden [4,8]. Distress extends along a continuum, ranging from common normal feeling of vulnerability and sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis [9]. High levels of informal caregiver distress may result in 1) patients having difficulties adjusting to their disease on the long-term, 2) patients who are influenced by informal caregiver's anxiety and thereby experiencing anxiety themselves 3) informal caregivers facing difficulties taking proper care of their significant other, for example administering medication and 4) informal caregivers with physical problems as a consequence of changes in functioning of their immune system and increased vulnerability for cardiovascular disease [10]. Sources for high levels of distress are different for every informal caregiver and may differ or change during patients' cancer trajectories. Common

sources of distress are associated with disruption of informal caregivers' own schedule and include treatment-related factors (treatment efficacy, managing side effects, lack of preparation providing complex care, patients' symptom distress), psychosocial factors (social isolation, role social functioning, feeling overwhelmed, helping the patient cope with emotional distress, complex family relationships) and/or arise from unmet needs (psychosocial, medical, financial, informational) [10]. It is known that women have a higher risk for distress than men [11]. The incidence of distress among informal caregivers of patients after cancer diagnosis is approximately 20% [12-14].

Distress can result in **depression** on the long-term. The National Cancer Institute defined depression as "a mental condition marked by ongoing feelings of sadness, despair, loss of energy, and difficulty dealing with normal daily life" [15]. People suffering from depression experience changes in their sleeping patterns, changes in appetite, loss of energy, anxiety, reduced concentration, restlessness, indecisiveness, feelings of guilt, hopelessness, worthlessness, thoughts of self-harm or suicide [16]. The prevalence of depressive symptoms among informal caregivers of cancer patients varies between 12 and 41% and partly depends on the (treatment) phase a patient is in [17-20].

Grief is described as "the normal response to a major loss, such as the death of a loved one" [21]. Generally spoken, on average the intensity of bereavement diminishes over time, without any intervention needed and grief becomes integrated in a person life. However, there is a group of individuals that suffers from **complicated grief**. Complicated grief has been defined as "a deviation from the normal (in cultural and societal terms) grief experience in either time course, intensity, or both, entailing a chronic and more intense emotional experience or an inhibited response, which either lacks the usual symptoms or in which onset of symptoms is delayed" [22]. These individuals experience problems in their personal life, as a consequence of the loss of a significant other, and natural recovery does not occur [6]. It is important to realize that symptoms of complicated grief resemble symptoms of depression and psychological distress [6]. Complicated grief may coincide with depression and worsening of depressive symptoms is often seen [6,22].

Health-related quality of life and fatigue

Taking care of a significant other has consequences for informal caregivers' **health-related quality of life** as well. In a study of Hays et al. health-related quality of life (HRQoL) is described as how health impacts on an individual's ability to function and his or her perceived well-being in physical, mental and social domains of life [23]. Research showed that a year after a patient is diagnosed with cancer, an

informal caregiver can have (negative) changes in neurohormonal and inflammatory processes due to stress [24]. Furthermore, associations between caring for a patient with cancer and increased risk for cardiovascular disease are found [25]. This impacts their health-related quality of life.

Another important problem that can impact informal caregivers' quality of life is **fatigue**. There is a definition of fatigue for patients with cancer, but for informal caregivers this definition does not apply. For informal caregivers the definition of the Oxford dictionary seems to be more applicable: "an extreme tiredness resulting from mental of physical exertion or illness". Although studies about this problem in informal caregivers are scarce, moderate to severe fatigue is reported. For example, Peters et al. describe that 23% of informal caregivers are moderate to severely fatigued during patients' palliative treatment [26]. Furthermore, sleep disturbances are a risk factor for developing depression [27] and fatigue impacts informal caregivers' daily activities which has implications for the support they can offer the patient [28]. Carter et al. even reported that 95% of informal caregiver of patients with advanced cancer experience sleep disturbances. They, however, did not use the prescribed sleep medication in order to stay available during the night to support the patient if they needed that [27]. Sleep disturbances may lead to fatigue and it is unknown how informal caregivers' fatigue is related to patients' difficulties, for example their fatigue or distress. Little research is performed concerning informal caregiver fatigue in relation to the problems they face when caring for their significant other.

Fear of recurrence

Fear of recurrence is a common problem among cancer survivors. It is defined as "fear, worry, or concern about cancer returning or progressing" [29]. The current prevalence of fear of cancer recurrence is on average 49% for cancer survivors [30]. Little is known about this concern among informal caregivers of cancer survivors. One study reports that 51% of partners of patients having prostate cancer fear that the cancer progresses (fear of progression). It is known that high levels of fear of recurrence among cancer survivors do not improve over time [31]. Moreover, higher levels of fear of recurrence are associated with poorer health behaviours, experiencing distress and increased use of health care utilities [30,32,33]. Considering these aspects, it seems important to study the levels of fear of recurrence further among informal caregivers of cancer survivors.

OUTLINE OF THE THESIS

This thesis is divided in **three parts**. The first part will focus on informal caregivers of patients on active treatment for cancer. The second part will focus on informal caregivers of patients after active treatment, i.e. cancer survivors and the third part will report on bereaved informal caregivers.

PART 1:
CARING FOR A PATIENT DURING THE TREATMENT PHASE

Informal caregivers of patients treated with curative intent

When a patient is treated with curative intent, it is important that the treatment will be completed in order to achieve the best results. Support of informal caregivers is therefore of great importance, which will help patients while receiving treatment. However, caring for a of patient treated for cancer can be burdensome, considering the intensity and the disruption of informal caregivers' personal lives.

Head and neck cancer

The incidence of head and neck cancer (HNC) in The Netherlands was 2839 cases in 2019 [2]. Of the newly diagnosed patients with HNC, approximately 50% is diagnosed with stage III or IV disease [34]. Squamous cell carcinoma is the most common type of HNC. Risk factors are tobacco and alcohol abuse. For patients with oropharyngeal cancer, part of the tumours are caused by the human papilloma virus (HPV) [35]. Patients with locally advanced HNC (i.e. stage III, IVa and IVb) are treated with curative intent, receiving concomitant chemoradiotherapy (accelerated radiotherapy with cisplatinum or cetuximab, depending on condition, age and / or kidney function) during six or seven weeks. Side effects that often occur during this treatment are, amongst others, (severe) fatigue, mucositis and dermatitis [36]. This has impact on patients' quality of life and may cause psychological **distress** [36-38]. Additionally, among patients with HNC the prevalence of a **major depressive disorder** is higher (approximately 40%) when compared to other groups of patients with cancer (approximately 12.5%) and the general population (approximately 3%) [39-41]. Getting support from their significant other is therefore indispensable, especially since completing this treatment gives them a chance of curation.

Supporting a patient during this intensive treatment may **burden** the informal caregiver and impact their mental and physical health. **Distress** is a common problem for informal caregivers after a patient is diagnosed with HNC [38,42]. Distress on the long-term can cause depression. Furthermore, it is obvious that the intense treatment with concomitant chemoradiotherapy, meaning almost daily visits to the outpatient clinic, can **fatigue** an informal caregiver. It is known that **fatigue** is associated with **distress** [27,28]. Although the number of studies with informal caregivers of patients treated for HNC is increasing, there is need for prospective studies to enhance understanding of caregivers' mental and physical health in relation to patients' problems and thereby support them properly [42].

Therefore, in **chapter 2** we present the results of a prospective study with informal caregivers of patients treated with concomitant chemoradiotherapy for locally advanced HNC. First, we explore the course of informal caregivers' burden and fatigue in relation to patients' fatigue, distress and health-related quality of life. Second, we search for risk factors for informal caregivers' burden and fatigue after patients' curative treatment with chemoradiotherapy.

Colon cancer

The incidence of colon cancer in the Netherlands in 2019 was 9237 cases [2]. Approximately 65% of the newly diagnosed patients with colon cancer, is diagnosed with stage II or III disease [43]. Patients with high risk stage II or stage III colon cancer are primarily treated with resection of the tumour, followed by adjuvant chemotherapy containing fluoropyrimidines and oxaliplatin (i.e. 5FU/leuvorin or capecitabine with oxaliplatin; CAPOX). Of this regimen, the most common side effects are hand-feet syndrome, nausea, vomiting, and sensory and peripheral neuropathy. Oxaliplatin is often discontinued prematurely, because the side effect of nerve damage may not be reversible and patients may develop chronic neuropathic problems.

In the Netherlands, Nijboer et al. studied informal caregivers of patients with newly diagnosed colorectal cancer who recently underwent surgery and had a prognosis of at least 6 months. They found that younger (<50 year) and female informal caregivers are more vulnerable and in need for more support [44]. Another finding of Nijboer et al. was that a more negative perception of caregiving is associated with a lower income level, living alone with the patient, high level of patient dependency, having a distressed relationship, and high involvement in caregiving tasks [45]. Nijboer et al. also described that caregivers belonging to these risk groups are more prone for longer-term depression, as were informal caregivers experiencing lower levels of emotional support [45]. I think we can

say that caring for a patient with colon cancer who is treated with curative intent can be **burdensome** and may cause **distress**. Additionally, it may impact informal caregivers' **health-related quality of life**. However, little is known about informal caregivers of patients treated with adjuvant chemotherapy after surgery. Informal caregiver support is vital as adjuvant chemotherapy further improves their prognosis.

Chapter 3 reports on a prospective study. First, we will investigate the course of caregiver burden and distress over time and identify the number of informal caregivers having higher levels of burden and distress. Second, we will search risk factors for developing higher levels of burden and distress during and after treatment. Third, we will explore whether informal caregivers' burden and distress is associated with patients' distress. Lastly, we will examine the course of caregivers' health-related quality of life over time and study how it is associated with their own burden and distress, and with distress of the patient.

Informal caregivers of patients on long-term treatment

When a patient undergoes long-term treatment, it is important that their support is stable and resilient during their treatment. One of the groups of patients on long-term treatment are patients with gastrointestinal stromal tumours. In 2018, the incidence and prevalence of GIST in the Netherlands was approximately 220 and 1360 cases, respectively [2]. GISTs belong to the rare and heterogenous group of soft tissue sarcomas. GISTs are known for their resistance to chemo- and radiotherapy and the survival used to be poor. In 2000 imatinib, a tyrosine kinase inhibitor (TKI), revolutionised the treatment of this disease with long-lasting responses in the metastatic setting leading to the registration of this drug in the metastatic setting, later followed by studies showing benefit in the adjuvant setting [46,47]. For recurrent/metastatic disease, this new treatment improved the median overall survival from less than one year to more than 5 years [46]. This changed patients' perspective significantly. A challenge for these patients on long-term cancer treatment is managing the side effects of treatment with TKIs such as fatigue, diarrhoea, nausea, periorbital oedema, muscle cramps and skin rash [48]. Furthermore, another common problem that patients with GIST face is fear of recurrence/progression [49]. This can impact informal caregivers as well [50]. During visits of patients and their informal caregivers to the outpatient clinic we observed that an informal caregiver can be as **distressed** as the patient treated with curative or palliative intent. Additionally, they do impress **burdened** as well. There are no studies yet which describe informal caregivers' burden and distress in the group of patients who are treated on the long-term for GIST.

Chapter 4 includes a cross-sectional, observational study to explore the level of informal caregivers' burden and distress during patients' long-term treatment with TKIs. Furthermore, we will also compare informal caregivers with high levels of distress and high levels of burden to informal caregivers with low levels of distress and low/moderate levels of burden. This in order to gain more insight in informal caregivers who are in need of more support.

PART 2: INFORMAL CAREGIVERS OF PATIENTS AFTER TREATMENT

Informal caregivers of patients in the survivorship phase

The incidence of prostate cancer was 12,646 cases in 2018 in The Netherlands [2]. For localized prostate cancer, active surveillance, radical prostatectomy or radiotherapy are options for treatment. The treatment of choice is made by considering the longer-term effects of the used modality and the preferences of the patient [51]. The 5-year survival for patients with stage I-III disease is between 96 and 100% [2]. Most of the patients adjust to their changed life after diagnosis, as do their informal caregivers. Nonetheless, **fear of cancer recurrence** is an important problem among cancer survivors and seems to also play a role in informal caregivers. However, this is not yet known for this group of informal caregivers, as is the relationship between fear of cancer recurrence and their **health-related quality of life**.

In **chapter 5** we describe a cross-sectional study of 1) the prevalence of informal caregivers' fear of recurrence, 2) differences in the percentage of high fear of cancer recurrence between informal caregivers and patients, 3) informal caregivers' demographics and survivors' clinical characteristics associated with high fear of cancer recurrence, and 4) the relationship between high fear of cancer recurrence and informal caregivers' health-related quality of life.

PART 3:
BEREAVED INFORMAL CAREGIVERS

Bereaved partners of patients treated in a phase I study

Patients participating in phase I clinical trials generally have no conventional- or later-phase clinical trial treatment options left. Their median survival is estimated nine months [52]. Participation in phase I clinical trials demands a good performance status. A limited chance of benefit could be expected when participating in these trials and side effects are seen, together with frequent visits to the outpatient clinic [53]. Considering this for patients in their end-of-life phase, critics question whether patients participate voluntarily and assume that their participation is a consequence of misconception and enforcement [54]. In contrast, there is literature reporting about patients who take a well-informed decision to participate, without coercion [55]. Clearly, participation has consequences for a patients' daily life, whether it is positive or negative. The studies performed were from the patients' and/or healthcare professionals' point of view. The point of view of patients' informal caregivers is at least as important, as an informal caregiver is faced with challenges during treatment as well. However, the informal caregivers' point-of-view was not actively sought.

In **Chapter 6** we will retrospectively, 1) explore how informal caregivers reflect on patients' participation in a phase I clinical trial after patients' death, and 2) determine their functioning in terms of **depression**, **distress**, **complicated grief** and **health-related quality of life** after a patients' death.

AIMS OF THE THESIS

The overall aim of this thesis is to gain more knowledge about informal caregivers' functioning when caring for a patient on (long-term) treatment for cancer, after treatment is ended or after a patients' death. The studies in this thesis aimed to give more insight in treatment phase-specific problems, like burden and distress during treatment, fear of recurrence after treatment and grief after a patients' death. The results will be used to evaluate how and when healthcare professionals can best provide support for caregivers in need during different phases of cancer treatment.

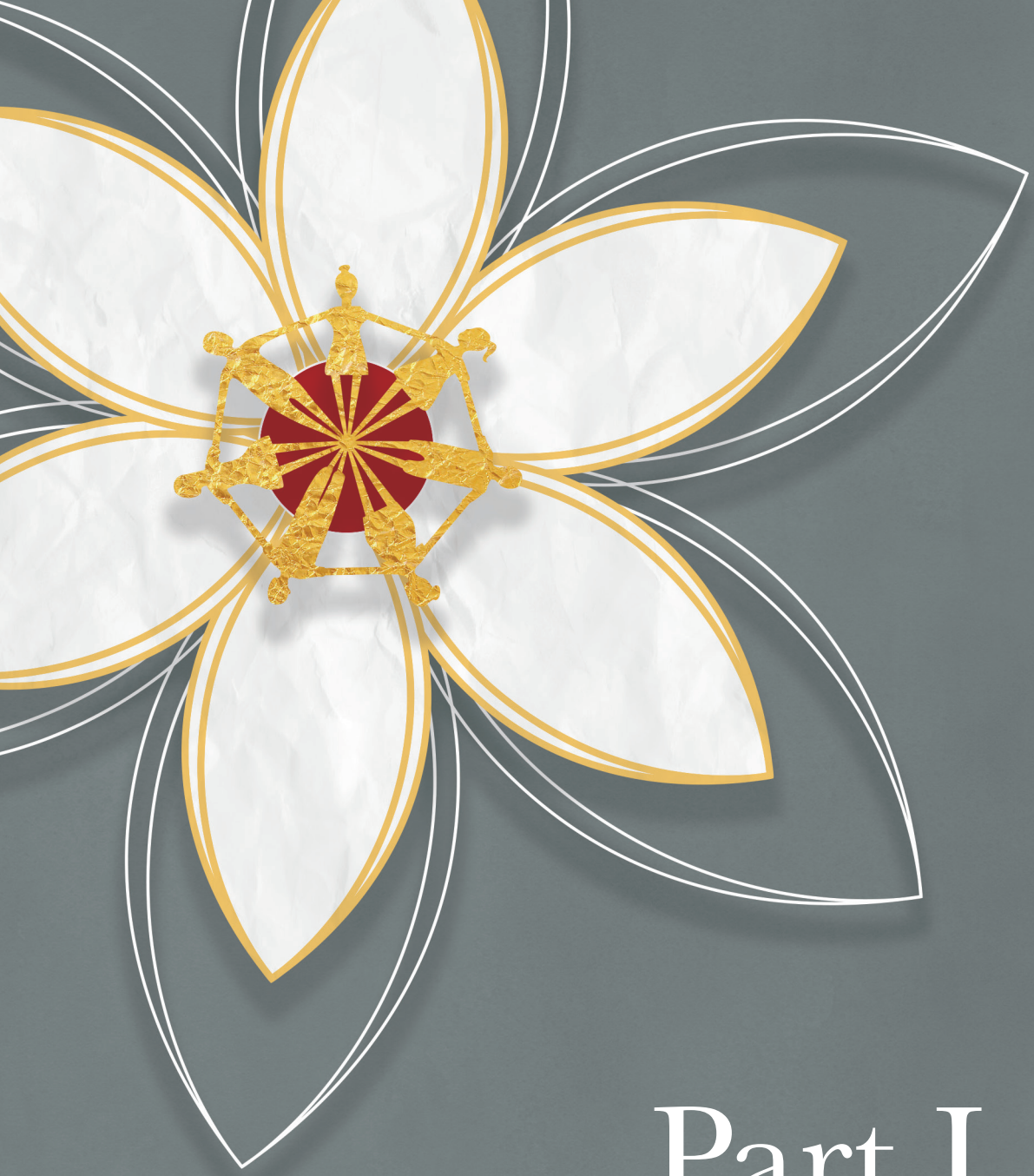
REFERENCES

1. Union for International Cancer Control - GLOBOCAN. (2018). https://www.uicc.org/news/new-global-cancer-data-globocan-2018.
2. Nederlandse Kankerregistratie https://www.cijfersoverkanker.nl/.
3. Sociaal cultureel planbureau - Voor elkaar? .
4. Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS (2014) Caregiver burden: a clinical review. JAMA : the journal of the American Medical Association 311 (10):1052-1060. doi:10.1001/jama.2014.304
5. Kim Y, Carver CS, Spillers RL, Love-Ghaffari M, Kaw CK (2012) Dyadic effects of fear of recurrence on the quality of life of cancer survivors and their caregivers. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 21 (3):517-525. doi:10.1007/s11136-011-9953-0
6. Simon NM (2013) Treating complicated grief. JAMA : the journal of the American Medical Association 310 (4):416-423. doi:10.1001/jama.2013.8614
7. Given BA, Given CW, Kozachik S (2001) Family support in advanced cancer. CA: a cancer journal for clinicians 51 (4):213-231
8. National Cancer Institute Dictionary of Cancer Terms - Definition of Distress. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/distress.
9. National Comprehensive Cancer Network.
10. Northouse LL, Katapodi MC, Schafenacker AM, Weiss D (2012) The impact of caregiving on the psychological well-being of family caregivers and cancer patients. Seminars in oncology nursing 28 (4):236-245. doi:10.1016/j.soncn.2012.09.006
11. Hodges LJ, Humphris GM, Macfarlane G (2005) A meta-analytic investigation of the relationship between the psychological distress of cancer patients and their carers. Social science & medicine 60 (1):1-12. doi:10.1016/j.socscimed.2004.04.018
12. Beesley VL, Price MA, Webb PM, Australian Ovarian Cancer Study G, Australian Ovarian Cancer Study-Quality of Life Study I (2011) Loss of lifestyle: health behaviour and weight changes after becoming a caregiver of a family member diagnosed with ovarian cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 19 (12):1949-1956. doi:10.1007/s00520-010-1035-2
13. Edwards B, Clarke V (2004) The psychological impact of a cancer diagnosis on families: the influence of family functioning and patients' illness characteristics on depression and anxiety. Psycho-oncology 13 (8):562-576. doi:10.1002/pon.773
14. Lewis FM, Fletcher KA, Cochrane BB, Fann JR (2008) Predictors of depressed mood in spouses of women with breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26 (8):1289-1295. doi:10.1200/JCO.2007.12.7159
15. National Cancer Institute Dictionary of Cancer Terms - Definition of Depression. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/depression.
16. World Health Organization. https://www.who.int/mental_health/management/depression/en/.
17. Guldin MB, Vedsted P, Zachariae R, Olesen F, Jensen AB (2012) Complicated grief and need for professional support in family caregivers of cancer patients in palliative care: a longitudinal cohort study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 20 (8):1679-1685. doi:10.1007/s00520-011-1260-3

18. Williams AL, Tisch AJ, Dixon J, McCorkle R (2013) Factors associated with depressive symptoms in cancer family caregivers of patients receiving chemotherapy. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 21 (9):2387-2394. doi:10.1007/s00520-013-1802-y
19. Lee Y, Lin PY, Chien CY, Fang FM (2015) Prevalence and risk factors of depressive disorder in caregivers of patients with head and neck cancer. Psycho-oncology 24 (2):155-161. doi:10.1002/pon.3619
20. Friethriksdottir N, Saevarsdottir T, Halfdanardottir SI, Jonsdottir A, Magnusdottir H, Olafsdottir KL, Guethmundsdottir G, Gunnarsdottir S (2011) Family members of cancer patients: Needs, quality of life and symptoms of anxiety and depression. Acta oncologica 50 (2):252-258. doi:10.3109/0284186X.2010.529821
21. National Cancer Institute Dictionary of Cancer Terms - Definition of Grief. https://www.cancer.gov/publications/dictionaries/cancer-terms/search/grief/?searchMode=Begins.
22. Stroebe M, Schut H, Stroebe W (2007) Health outcomes of bereavement. Lancet 370 (9603):1960-1973. doi:10.1016/S0140-6736(07)61816-9
23. Hays RD, Morales LS (2001) The RAND-36 measure of health-related quality of life. Ann Med 33 (5):350-357. doi:10.3109/07853890109002089
24. Rohleder N, Marin TJ, Ma R, Miller GE (2009) Biologic cost of caring for a cancer patient: dysregulation of pro- and anti-inflammatory signaling pathways. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27 (18):2909-2915. doi:10.1200/JCO.2008.18.7435
25. Northouse L, Williams AL, Given B, McCorkle R (2012) Psychosocial care for family caregivers of patients with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30 (11):1227-1234. doi:10.1200/JCO.2011.39.5798
26. Peters ME, Goedendorp MM, Verhagen SA, Smilde TJ, Bleijenberg G, van der Graaf WT (2014) A prospective analysis on fatigue and experienced burden in informal caregivers of cancer patients during cancer treatment in the palliative phase. Acta oncologica:1-7. doi:10.3109/0284186X.2014.953254
27. Carter PA, Chang BL (2000) Sleep and depression in cancer caregivers. Cancer nursing 23 (6):410-415
28. Jensen S, Given B (1993) Fatigue affecting family caregivers of cancer patients. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 1 (6):321-325
29. Lebel S, Maheu C, Tomei C, Bernstein LJ, Courbasson C, Ferguson S, Harris C, Jolicoeur L, Lefebvre M, Muraca L, Ramanakumar AV, Singh M, Parrott J, Figueiredo D (2018) Towards the validation of a new, blended theoretical model of fear of cancer recurrence. Psycho-oncology 27 (11):2594-2601. doi:10.1002/pon.4880
30. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, Ozakinci G (2013) Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv 7 (3):300-322. doi:10.1007/s11764-013-0272-z
31. Savard J, Ivers H (2013) The evolution of fear of cancer recurrence during the cancer care trajectory and its relationship with cancer characteristics. Journal of psychosomatic research 74 (4):354-360. doi:10.1016/j.jpsychores.2012.12.013
32. Lebel S, Tomei C, Feldstain A, Beattie S, McCallum M (2013) Does fear of cancer recurrence predict cancer survivors' health care use? Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 21 (3):901-906. doi:10.1007/s00520-012-1685-3

33. Fisher A, Beeken RJ, Heinrich M, Williams K, Wardle J (2016) Health behaviours and fear of cancer recurrence in 10 969 colorectal cancer (CRC) patients. Psycho-oncology 25 (12):1434-1440. doi:10.1002/pon.4076
34. Dutch Institute for Clinical Auditing - Dutch Head and Neck Audit. https://dica.nl/jaarrapportage-2017/dhna.
35. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363 (1):24-35. doi:10.1056/NEJMoa0912217
36. Argiris A, Karamouzis MV, Raben D, Ferris RL (2008) Head and neck cancer. Lancet 371 (9625):1695-1709. doi:10.1016/S0140-6736(08)60728-X
37. Bottomley A, Tridello G, Coens C, Rolland F, Tesselaar ME, Leemans CR, Hupperets P, Licitra L, Vermorken JB, Van Den Weyngaert D, Truc G, Barillot I, Lefebvre JL (2014) An international phase 3 trial in head and neck cancer: quality of life and symptom results: EORTC 24954 on behalf of the EORTC Head and Neck and the EORTC Radiation Oncology Group. Cancer 120 (3):390-398. doi:10.1002/cncr.28392
38. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, Kuik DJ, de Bree R, Leemans CR (2007) Distress in spouses and patients after treatment for head and neck cancer. The Laryngoscope 117 (2):238-241. doi:10.1097/01.mlg.0000250169.10241.58
39. Lydiatt WM, Moran J, Burke WJ (2009) A review of depression in the head and neck cancer patient. Clinical advances in hematology & oncology : H&O 7 (6):397-403
40. Sehlen S, Lenk M, Herschbach P, Aydemir U, Dellian M, Schymura B, Hollenhorst H, Duhmke E (2003) Depressive symptoms during and after radiotherapy for head and neck cancer. Head & neck 25 (12):1004-1018. doi:10.1002/hed.10336
41. Bortolato B, Hyphantis TN, Valpione S, Perini G, Maes M, Morris G, Kubera M, Kohler CA, Fernandes BS, Stubbs B, Pavlidis N, Carvalho AF (2017) Depression in cancer: The many biobehavioral pathways driving tumor progression. Cancer Treat Rev 52:58-70. doi:10.1016/j.ctrv.2016.11.004
42. Longacre ML, Ridge JA, Burtness BA, Galloway TJ, Fang CY (2012) Psychological functioning of caregivers for head and neck cancer patients. Oral oncology 48 (1):18-25. doi:10.1016/j.oraloncology.2011.11.012
43. Dutch Institute for Clinical Auditing - Dutch ColoRectal Audit. https://dica.nl/jaarrapportage-2018/dcra.
44. Nijboer C, Triemstra M, Tempelaar R, Mulder M, Sanderman R, van den Bos GA (2000) Patterns of caregiver experiences among partners of cancer patients. The Gerontologist 40 (6):738-746
45. Nijboer C, Triemstra M, Tempelaar R, Sanderman R, van den Bos GA (1999) Determinants of caregiving experiences and mental health of partners of cancer patients. Cancer 86 (4):577-588
46. Joensuu H, Wardelmann E, Sihto H, Eriksson M, Sundby Hall K, Reichardt A, Hartmann JT, Pink D, Cameron S, Hohenberger P, Al-Batran SE, Schlemmer M, Bauer S, Nilsson B, Kallio R, Junnila J, Vehtari A, Reichardt P (2017) Effect of KIT and PDGFRA Mutations on Survival in Patients With Gastrointestinal Stromal Tumors Treated With Adjuvant Imatinib: An Exploratory Analysis of a Randomized Clinical Trial. JAMA Oncol 3 (5):602-609. doi:10.1001/jamaoncol.2016.5751
47. Joensuu H (2012) Adjuvant therapy for high-risk gastrointestinal stromal tumour: considerations for optimal management. Drugs 72 (15):1953-1963. doi:10.2165/11635590-000000000-00000

48. Sodergren SC, White A, Efficace F, Sprangers M, Fitzsimmons D, Bottomley A, Johnson CD (2014) Systematic review of the side effects associated with tyrosine kinase inhibitors used in the treatment of gastrointestinal stromal tumours on behalf of the EORTC Quality of Life Group. Crit Rev Oncol Hematol 91 (1):35-46. doi:10.1016/j.critrevonc.2014.01.002
49. Custers JA, Tielen R, Prins JB, de Wilt JH, Gielissen MF, van der Graaf WT (2015) Fear of progression in patients with gastrointestinal stromal tumors (GIST): Is extended lifetime related to the Sword of Damocles? Acta oncologica 54 (8):1202-1208. doi:10.3109/0284186X.2014.1003960
50. van de Wal M, Langenberg S, Gielissen M, Thewes B, van Oort I, Prins J (2017) Fear of cancer recurrence: a significant concern among partners of prostate cancer survivors. Psycho-oncology 26 (12):2079-2085. doi:10.1002/pon.4423
51. European Association of Urology - guideline prostate cancer.
52. Wheler J, Tsimberidou AM, Hong D, Naing A, Jackson T, Liu S, Feng L, Kurzrock R (2009) Survival of patients in a Phase 1 Clinic: the M. D. Anderson Cancer Center experience. Cancer 115 (5):1091-1099. doi:10.1002/cncr.24018
53. Catt S, Langridge C, Fallowfield L, Talbot DC, Jenkins V (2011) Reasons given by patients for participating, or not, in Phase 1 cancer trials. European journal of cancer 47 (10):1490-1497. doi:10.1016/j.ejca.2011.02.020
54. Agrawal M, Emanuel EJ (2003) Ethics of phase 1 oncology studies: reexamining the arguments and data. JAMA: the journal of the American Medical Association 290 (8):1075-1082. doi:10.1001/jama.290.8.1075
55. Agrawal M, Grady C, Fairclough DL, Meropol NJ, Maynard K, Emanuel EJ (2006) Patients' decision-making process regarding participation in phase I oncology research. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24 (27):4479-4484. doi:10.1200/JCO.2006.06.0269



Part I

Caring for a patient
during the treatment phase

Chapter 2

Caregivers' burden and fatigue during and after patients' treatment with concomitant chemoradiotherapy for locally advanced head and neck cancer: a prospective, observational pilot study

Simone M.C.H. Langenberg, Carla M.L. van Herpen, Claudia C.M. van Opstal, Anke N.M. Wymenga, Winette T.A. van der Graaf, Judith B. Prins

Supportive Care in Cancer (2019) 27: 4145–4154

ABSTRACT

Introduction: Knowledge of caregivers' burden and fatigue before and after patients' treatment for locally advanced head and neck cancer is scarce. Therefore, we aimed to explore caregivers' fatigue and burden in relation to patients' fatigue, distress and health-related quality of life (HRQOL).

Methods: For caregivers, burden and fatigue were assessed. For patients, fatigue severity, distress and health-related quality of life was assessed. Measurements were conducted prior to treatment, 1 week and 3 months after chemoradiotherapy.

Results: Caregivers' burden and fatigue followed patients' high peak in distress, fatigue and diminished HRQOL as a consequence of treatment. Caregivers' baseline fatigue was a predictor for fatigue after chemoradiotherapy. Being a female spouse with higher baseline levels of fatigue and burden and caring for a patient with lower levels of HRQOL seem risk factors for burden after chemoradiotherapy.

Conclusions: Attention should be paid to caregivers' burden and fatigue before starting patients' intense treatment with chemoradiotherapy, as both burden and fatigue before starting treatment may contribute to burden and fatigue after chemoradiotherapy.

INTRODUCTION

Every year, globally 650,000 patients are diagnosed with head and neck cancer. The most common type of head and neck cancer is head and neck squamous cell carcinoma (HNSCC) which is associated with tobacco and alcohol abuse. Furthermore, in oropharyngeal cancer part of the tumours are caused by the human papillomavirus (HPV). Patients with HPV positive tumours have a favourable prognosis when compared to patients with HPV negative tumours [1]. Standard treatment in patients with locally advanced head and neck cancer (LAHNC) is concomitant chemoradiotherapy with curative intent. This is an intensive treatment accompanied with (visible) consequences and side effects such as severe fatigue, mucositis and dermatitis [2], which negatively influences the patients' quality of life and may cause psychological distress [2-4]. Patients with head and neck cancer differ from other cancer patients, as the prevalence of major depressive disorder is the highest among head and neck cancer patients [5].

Considering the aforementioned aspects, social support from patients' informal caregivers is indispensable during and after treatment. Badr and colleagues found that patients with head and neck cancer and their caregiver cope with distress as a couple [6]. Consequently, caregivers can be burdened by care for their significant other. Lazarus and Folkman introduced the stress theory and described the construct of "appraisal" [7]. This as a cognitive process of an individual to balance environmental demands or stressors in relation to their personal life. This theory and the construct of appraisal is often used in caregiver literature, as burden can be an outcome of this appraisal [8,9]. Caregiver burden is described by Zarit and colleagues as the extent to which giving care to a significant other is perceived with an adverse effect on their emotional, social, financial, physical, and spiritual functioning [10]. Adelman and colleagues describe that this definition emphasizes the multidimensional toll caregiving may demand on care providers and that giving care to a significant other is a highly individualized experience [11]. Psychopathology may arise when there is an imbalance between demands and caregivers' personal life [8]. High levels of caregiver burden may remain high after ending treatment, which is shown in a study with caregivers of patients treated for stage II and III oesophageal cancer [12]. Studies performed amongst caregivers of patients with head and neck cancer show that head and neck cancer caregivers have poorer mental health, with higher distress levels when compared to the general population and compared to head and neck cancer patients themselves [13,14]. Risk factors for poorer mental health and burden are being female, providing more hours of care, having disrupted social

interaction, have disrupted self-care and an increased need for patients' support [15]. Additionally, fatigue is a frequently mentioned physical symptom of burden and is likely to coincide with burden, which is sparsely studied among caregivers of patients with cancer [16], and not yet studied in this group of caregivers.

This prospective, observational pilot study had two exploratory aims. First, we wanted to explore the course of caregivers' burden and fatigue in relation to patients' fatigue, distress and HRQoL before and after chemoradiotherapy. An important number of caregivers of head and neck cancer patients report need for help themselves [17]. Therefore, we aim to identify caregivers with a high level of burden and fatigue and we want to investigate when the levels of burden and fatigue are at their highest. This in order to identify when support seems to be needed most. Second, we aimed to explore risk factors for developing higher levels of burden and fatigue of caregivers after patients' treatment with chemoradiotherapy. Based on clinical observations of informal caregivers of patients treated for LAHNC and based on known risk factors for care-related problems supporting a patient with cancer, we think that female gender [18], younger age [18,19] and being in a spousal relationship with the patient [19-21], caregivers' higher baseline role problems [22] and caregivers of patients with worse HRQoL [9,23,24] have a higher risk for higher levels of burden and fatigue after ending treatment for LAHNC.

MATERIALS AND METHODS

Setting and participants

This prospective, observational pilot study was conducted between 2011 and 2013 at the Radboud university medical center in the Netherlands. Eligible for participation were patients older than 18 years with LAHNC and who were scheduled for treatment with chemoradiotherapy with curative intent (stadium III, IVa, IVb), and their informal caregivers. Patients and caregivers had to be able to give informed consent and read and write in Dutch. Patients receiving the chemoradiotherapy as primary treatment were treated with concomitant chemoradiotherapy during 5.5 weeks. They received accelerated radiotherapy. Patients who were treated with concomitant chemoradiotherapy as postoperative therapy were treated with a conventional chemoradiotherapy schedule and received treatment for 7 weeks. In oropharyngeal cancer patients, HPV positivity was determined by the use of immunohistochemical determination of p16. In case p16 was positive, PCR for HPV was performed. If also the PCR was positive we identified the patient as HPV positive.

Procedure

The local medical ethical committee gave permission for the study. The attending oncologist (CH) and/or nurse practitioner (CO) informed the couples during their first visit to the outpatient clinic. If both patient and caregiver gave their informed consent, they were included. The attending oncologist or nurse practitioner extracted the treatment characteristics from the patient's medical record, including HPV status, postoperative chemoradiotherapy (yes/no) and duration of treatment (weeks). Participants were asked to complete self-report questionnaires at three time points: (T0) prior to start chemoradiotherapy, (T1) one week after ending chemoradiotherapy, and (T2) three months after the end of chemoradiotherapy. Completing the paper and pencil questionnaire took between 45 and 60 minutes.

Questionnaires

A general questionnaire assessed caregivers' and patients' demographic characteristics, including gender, age, nationality, education and employment.

Caregiver burden

Caregivers' burden was assessed by the Self-Perceived Pressure from Informal Care questionnaire (SPPIC), which is a Dutch, validated questionnaire [8]. It measures how personal interests (i.e. possibility to have own thoughts, activities and/or other roles they want to fulfil in life) interfere with the pressure they perceive as a consequence of giving care to a significant other. Examples of questions are "As a consequence of the situation of my significant other, less time is available managing my personal life" and "Combining the responsibility for my significant other and my family and work is challenging". It consists of nine items and is scored on a 5-point Rasch scale. According to the manual of the questionnaire, the scores are dichotomized to 0 ("no!" and "no") and 1 ("yes!", "yes" and "more or less"), and scores range from 0 to 9. Higher scores indicate higher levels of caregivers' burden. Total scores on the scale were defined as low (0-3), moderate (4-6) and high levels of burden (7-9) [12]. The internal consistency of the questionnaire in this sample was sufficient (α=0.74).

Patient psychological distress and quality of life

Patients completed The Hospital Anxiety and Depression Scale (HADS) [25], which is a 14-item self-assessment questionnaire to assess psychological distress. Each item is rated on a scale from 0 (not at all) to 3 (very much). Total scores range between 0 and 42, with higher scores indicating higher distress. A cutoff score of 11 was used for detecting manifest distress [26]. The scale has been translated and validated in the Dutch general population and showed a good internal consistency (α=0.82 – 0.90) [27].

The EORTC QLQ-C30 (version 3.0) is a well-validated questionnaire to assess HRQoL.[28] It consists of five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, pain, nausea), six single item scales (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, financial impact) and the global HRQoL scale. Final scores range between 0 and 100. Higher scores of the functional scales representing better functioning and higher levels of the symptoms scales representing more symptoms. The internal consistency of this questionnaire is good (α=0.84) [28]. We decided to only use the global HRQoL scale in our exploratory analyses, as this variable gives a more overall view of the well-being while treated with chemoradiotherapy. An increase or decrease of 10 points or more on the subscale global HRQoL is regarded as a clinically relevant change [29]. Additionally, the EORTC QoLQ-H&N35 (head and neck module) which assesses treatment-related symptoms; six symptom scales (pain, swallowing, senses, speech, social eating, social contact, sexuality), six symptom items (problems with teeth, problems with opening mouth, sticky saliva, coughing, feeling ill), five additional items (pain medication use, nutritional supplement use, feeding tube, changes in body weight). Higher scores indicate more symptoms. The internal consistency of the subscales is good (α=0.72 – 0.95) [28].

Caregiver and patient fatigue

For caregivers and patients, the severity of fatigue was assessed by the validated subscale fatigue severity of the Checklist Individual Strength (CIS). The 8-item subscale is scored on a 7-point Likert scale. The final score ranges from 8 to 56. Higher scores indicating more fatigue [30]. A cutoff score of 35 and higher was used to indicate severe fatigue. This cutoff score was validated in healthy subjects in the general population and patients with chronic fatigue [31]. The cutoff was used in different studies with patients in different phases of treatment for cancer and caregivers, and shows that the scale is sensitive to change in levels of fatigue over time [32-34]. The internal consistency of the subscale is good (α=0.88) [30].

Statistical analyses

Analyses were performed using Statistical Package for the Social Sciences software version 20 (SPSS Inc. Chicago, IL, USA). When the data of the patient and/or the caregiver were incomplete at any time point, the dyad was excluded for analyses. For sample characteristics, descriptive statistics were used. For continuous variables Student's t-tests (equal distribution expected between groups) or the Mann-Whitney U test (equal distribution unlikely) were used. For categorical variables, Chi-square tests or Fisher's exact test were performed. Characteristics of dyads

who dropped out during the study were compared with the dyads who completed all the measurements. This was performed for age, gender, marital status, level of education, patients' and caregivers' baseline fatigue, caregivers' baseline burden and patients' HRQoL and distress.

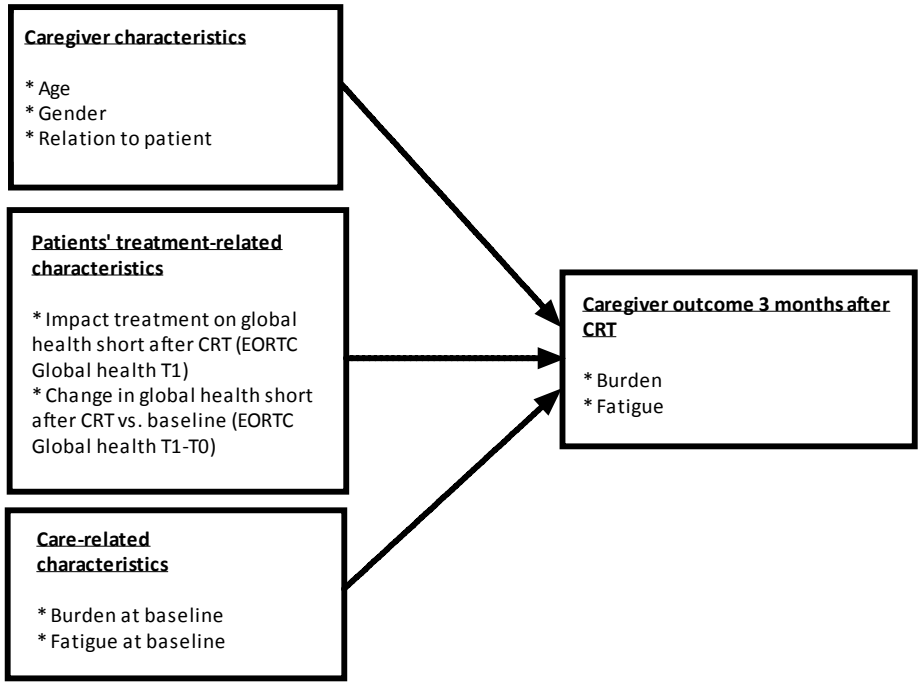


Figure 1. Research model for predicting factors contributing to burden and fatigue of informal caregivers after patients' chemoradiotherapy

For our first exploratory aim, general linear model repeated measure analysis was performed to determine caregivers' course of burden, using mean SPPIC scores on all measurement time points (T0, T1 and T2). For determining caregivers' and patients' course of fatigue, mean fatigue severity scores on all measurement time points (T0, T1 and T2) were used. Additionally, the same analyses were performed to determine caregivers' fatigue in relation to patients' fatigue, using mean scores on all the measurement time points (T0, T1 and T2). To explore the association between patients' distress and caregivers' burden and distress, Pearson correlations were performed. For our second exploratory aim, we designed an exploratory model, which is shown in Figure 1. Linear regression analyses (enter method) were conducted based on the exploratory model. Fatigue and burden on

T2 were used as dependent variables. Independent variables were age, gender, relation to the patient, patients' HRQoL on T1, patients' difference in HRQoL between T1 and T0, caregivers' baseline burden and caregivers' baseline fatigue. The adjusted R^2 and Beta weights were used for interpretation of the model. The assumptions of linearity, constant error variance and normality were determined performing residual analysis. Statistical significance was determined based on a two-sided alpha of 0.05.

RESULTS

Caregivers' and patients' baseline characteristics

In total, 68 patients were eligible. Eight dyads decided not to participate. Reasons not to participate were that participating was perceived too burdensome (n=4), patient had caregivers, but no principal one (n=2), dyad was not recruited by accident (n=1) or reasons were unclear (n=1). After inclusion, three dyads withdrew from participation for unclear reasons and one patient passed away. The mean recruitment rate was three dyads every month. For analyses, complete data of 56 dyads was available for T0, 49 dyads for T1 (withdrew n=3; incomplete data n=1; patient deceased n=1, recurrent disease n=1, reason unclear n=1), and 45 dyads for T2 (recurrent disease n=2, logistic mistake (n=1), incomplete data n=1). Baseline characteristics are given in Table 1. For age, gender, marital status, level of education and baseline fatigue, no significant differences were found between caregivers who dropped out (n=11) and those who completed all assessments at all time points (n=45), except for baseline burden, which was significantly lower in the group who dropped out (mean rank 16.6) compared to the group who completed all measurements (mean rank 31.4; p=0.006). Patients who dropped out (n=11) showed no significant differences compared to the patients who completed all measurements (n=45), except for baseline HRQoL, which was significantly higher in the group of patients who dropped out (mean rank 37.6) compared to the patients who completed all measurements (mean rank 25.5; p=0.03). At T0, patients' health-related functioning was significantly better and disease-related symptoms were significantly less when compared with data of the EORTC manual reference values (stage III/IV head and neck cancer) [35]. Details are outlined in Table 2.

Table 1. Sample characteristics

Characteristics		Caregiver, n (%)	Patient, n (%)
Participants		56	56
Gender	Female, n (%)	42 (75)	19 (34)
	Male, n (%)	14 (25)	37 (66)
Median age, years (ICR)		58 (44-64)	58 (53-63)
Education level (ISCED)	Lower education ≤ 4, n (%)	44 (80)	43 (78)
	Higher education > 4, n (%)	11 (20)	12 (22)
Relation to patient	Partner, n (%)	39 (70)	-
	Parent, n (%)	5 (9)	-
	Child, n (%)	7 (13)	-
	Friend, n (%)	3 (5)	-
	Other, n (%)	2 (4)	-
Employment status	Employed (paid), n (%)	32 (58)	26 (47)
	Unemployed, n (%)	0 (0)	7 (13)
	Housekeeper, n (%)	12 (22)	8 (14.5)
	Disablement insurance act, n (%)	2 (4)	6 (11)
	Retired, n (%)	9 (16)	8 (14.5)
Duration of treatment	Weeks, median (IQR)	-	5.5 (5–6)
Chemoradiotherapy (CRT)	Postoperative CRT (%)	-	42.9
	Primary CRT (%)	-	57.1
HPV status	Positive, n (%)	-	5 (8.9)

ISCED = International Standard Classification of Education 2011; ≤ 4: secondary, non-tertiary education level, > 4: tertiary education level (bachelor, master or doctoral level); HPV = human papilloma virus

Caregivers' course of burden and fatigue and patients' course of fatigue, distress and HRQoL

Caregivers' mean scores on burden and the distribution of the level of burden are given in Table 3. Caregivers' mean scores of burden changed significantly over time (p=0.006), and showed a peak at T1. At T2 after chemoradiotherapy, burden was significantly lower when compared to burden at T0 and T1 (p=0.024 and p=0.001, respectively). Caregivers' mean scores on fatigue and the proportion of severely fatigued caregivers are shown in Table 3. Caregivers' decrease from T1 to T2 was significant (p=0.029).

Table 2. EORTC mean scores of sample, compared to reference data [35]

QLQ-C30	Reference data (n=1722); head and neck cancer stage III-IV, mean (SD)	Baseline Scores patients (n=56)	Sign. (p-value)
Global health-related QoL	63.1 (22.4)	73.3 (19.7)	<0.001[a]
Physical functioning	81.2 (20.2)	87.0 (14.0)	0.004[a]
Role functioning	78.8 (27.9)	72.2 (29.8)	0.111
Emotional functioning	71.2 (24.1)	78.2 (17.5)	0.005[a]
Cognitive functioning	86.4 (19.1)	89.8 (19.3)	0.198
Social functioning	82.2 (24.7)	77.8 (25.5)	0.208
Fatigue	27.6 (25)	21.8 (20.2)	0.04[a]
Nausea and vomiting	5.2 (13.3)	1.9 (7.0)	0.001[a]
Pain	24.9 (26.3)	21.6 (26.4)	0.364
Dyspnoea	18.0 (26.6)	6.9 (16.5)	<0.001[a]
Insomnia	28.5 (32.4)	26.5 (29.2)	0.625
Appetite loss	19.4 (29.3)	8.6 (20.7)	<0.001[a]
Constipation	11.7 (23.2)	8.0 (18.2)	0.145
Diarrhoea	6.1 (16.7)	4.3 (13.0)	0.32
Financial difficulties	18.8 (30.2)	13.2 (13.0)	0.106
QLQ-HN-35			
Pain	29.9 (25.1)	21.3 (19.1)	0.002[a]
Swallowing	27.5 (26.1)	17.8 (23.8)	0.005[a]
Senses	20.0 (30.0)	9.8 (17.1)	<0.001[a]
Speech	27.1 (27.2)	16.9 (19.7)	<0.001[a]
Social eating	23.9 (26.7)	13.0 (14.4)	<0.001[a]
Social contact	13.2 (19.1)	7.7 (13.0)	0.004[a]
Sexuality	32.3 (36.1)	28.1 (21.8)	0.31
Teeth	27.8 (35.0)	10.2 (21.7)	<0.001[a]
Opening mouth	22.4 (31.9)	30.1 (33.2)	0.099
Dry mouth	31.1 (34.2)	19.2 (23.2)	0.001[a]
Sticky saliva	32.4 (35.4)	20.9 (24.0)	0.001[a]
Coughing	34.9 (32.1)	17.7 (26.1)	<0.001[a]
Felt ill	21.7 (29.2)	10.3 (19.3)	<0.001[a]
Pain killers	52.8 (49.9)	61.5 (49.1)	0.205
Nutritional supplements	27.0 (44.4)	28.9 (45.7)	0.772
Feeding tube	18.3 (38.7)	7.6 (26.7)	0.005[a]
Weight loss	41.3 (49.2)	34.6 (48.0)	0.32
Weight gain	25.9 (43.8)	36.5 (48.6)	0.121

[a] Statistically significant difference

Table 3. Mean scores for caregivers' burden and fatigue and distribution on individual level (> cutoff)

Time point	T0 (n=56)	T1 (n=47)	T2 (n=45)
Mean scores (SD)			
Fatigue	24.3 (13)	27.5 (12.4)	22.4 (11.8)
Burden	4.1 (2.4)	4.6 (2.4)	3.2 (2.4)
Score > cutoff n (%)			
Fatigue	10 (19)	14 (30)	9 (21)
Burden			
Low	30 (53.6)	20 (42.6)	30 (66.7)
Moderate	20 (35.7)	17 (63.2)	10 (22.2)
High	6 (10.7)	10 (21.3)	5 (11.1)

There was no statistically significant difference for caregiver found between groups for HPV positivity on all three time points for burden (T0: mean rank 40.6 versus 27.3, p=0.079; T1: mean rank 27.2 versus 23.6, p=0.578; T2: mean rank 32.2 versus 21.9, p=0.093) and fatigue (T0: mean rank 35.3 versus 26.7, p=0.243; T1: mean rank 26.2 versus 23.7, p=0.704; T2: mean rank 29.7 versus 20.9, p=0.144).

Patients' mean scores on fatigue, distress and global health are shown in Table 4. Patients' fatigue increased significantly from T0 to T1 (p<0.001), and decreased significantly from T1 to T2 (p<0.001). Patients' levels of fatigue were significantly higher at T2 compared to T0 (p=0.026). Patients' distress changed over time (p=0.012), and showed a peak at T1. Distress increased between T0 and T1 (p=0.02), and decreased again between T1 and T2 (p=0.03), down to baseline levels. There was no difference in distress at T0 and T2. Patients' HRQoL decreased from T0 to T1 (p<0.001), and recovered from T1 to T2 (p<0.001), up to baseline levels. Moreover, a clinically relevant decrease in HRQoL was observed from T0 to T1 (>10 points; from 73.3 to 54.3; range 0-100), and this was restored from T1 to T2 (> 10 points; from 54.3 to 72.0; range 0-100).

Comparing the course of caregivers' fatigue to patients' fatigue, patients were significantly more fatigued than their caregivers (F[1,81] = 5.245, p=0.025). Fatigue peaked for both patients and caregivers at T1 (F[1,81] = 39.153, p<0.001). Patients' fatigue was lower at baseline but increased significantly faster (F[1,81] = 9.233, p=0.003).

Table 4. Mean scores of patients' fatigue, distress and HRQoL and proportion of patients' fatigue severity and distress.

Time point	T0 (n=56)	T1 (n=47)	T2 (n=45)
Mean scores (SD)			
Fatigue	23.7 (12.1)	37.8 (12.7)	28.1 (12.7)
Distress	10.4 (7.3)	13.2 (9.0)	10.7 (6.8)
Global health	73.3 (19.7)	54.3 (25.0)	72.0 (15.7)
Score > cutoff n (%)			
Fatigue	9 (16)	31 (65)	14 (33)
Distress	25 (46)	26 (54)	25 (56)

Correlations

At baseline, caregivers' burden was significantly correlated to patients' fatigue, distress and HRQoL ($r=0.28$, $p=0.04$ and $r=0.32$, $p=0.02$ and $r=-0.331$, $p=0.02$, respectively). At T1, caregivers' burden was significantly correlated to patients' distress and HRQoL ($r=0.47$, $p=0.001$ and $r=-0.44$, $p=0.002$). At T2, burden was significantly correlated to patients' distress and HRQoL at T2 ($r=0.411$, $p=0.005$ and $r=-0.413$, $p=0.005$).

At baseline, caregivers' fatigue was significantly correlated to patients fatigue at T0 ($r=0.31$, $p=0.03$). Patients' fatigue at T0 was significantly correlated to distress and HRQoL at T0 ($r=0.452$, $p=0.001$ and $r=-0.657$, $p < 0.001$, respectively), T1 ($r=0.623$, $p<0.001$ and $r=-0.723$, $p<0.001$, respectively) and T2 ($r=0.314$, $p=0.04$ and $r=-0.616$, $p<0.001$, respectively).

Patients' distress was significantly correlated to their HRQoL at T0, T1 and T2 ($r=-0.564$, $p<0.001$, $r=-0.725$, $p<0.001$ and $r=-0.508$, $p<0.001$, respectively). Caregivers' fatigue on T0, T1 and T2 was significantly correlated at all time points ($r=0.43$, $p=0.001$, $r=0.51$, $p<0.001$ and $r=0.54$, $p<0.001$, respectively).

Exploration of risk factors for burden and fatigue after chemoradiotherapy

Table 5 shows the results of the regression analysis. Twenty-seven percent of the variance in scores for burden on T2 could be explained by the independent variables. There was no significant attribution of one individual independent variable. However, all seven variables together, i.e. younger age, spousal and female caregivers, higher levels of fatigue and burden on baseline within caregiver and greater difference in decline in HRQoL within the patient, were found to contribute significantly ($p=0.012$). Burden and fatigue at baseline contributed most to burden three months after chemoradiotherapy (13% of the 27%), followed by gender, patients' global HRQoL at T1, and relation to the patient. Age and the change in global HRQoL between T1 and T0 contributed less.

Thirty-four percent of the variance in fatigue scores was explained by the independent variables. Caregivers' fatigue at baseline contributed significantly to caregivers' fatigue on T2 ($p<0.01$). Caregivers' care-related characteristics (i.e. burden and fatigue) at baseline contributed most to the explained variance of fatigue scores three months after chemoradiotherapy (29% of 34%).

Table 5. Determinants of burden and fatigue among caregiver of patients with LAHNC, 3 months after completing chemoradiotherapy; final ß weight and adjusted R^2 (n=41)

Caregiver characteristics	Burden	Fatigue
Gender (male=0; female=1)	0.234	0.067
Age	0.059	0.065
Relation to patient (non-spouse=0; spouse=1)	0.218	-0.023
Adjusted R^2	**0.08**	**0.01**
Patient characteristics - treatment related		
EORTC GH T1	-0.222	0.023
EORTC GH T1-T0	0.058	0.25
ΔAdjusted R^2	**0.06**	**0.04**
Caregiver care-related characteristics		
Baseline burden	0.267	-0.009
Baseline fatigue	0.262	0.609[a]
Δ Adjusted R^2	**0.13**	**0.29**
Total R^2	**27%**	**34%**

[a] $p<0.01$

DISCUSSION

This prospective, observational pilot study of patients with LAHNC and their caregivers is one of the few studies to focus on the course of burden and fatigue of caregivers in relation to patients fatigue, distress and global HRQoL. It contributes to the existing knowledge about risk factors for burden and fatigue in caregivers of patients short after patients' end of treatment with chemoradiotherapy.

This study adds valuable knowledge for the identification of caregivers at risk for burden when patients have finished chemoradiotherapy. Female spouses with higher baseline levels of burden and fatigue, and caring for patients with lower levels of global HRQoL seem at higher risk for burden after end of the intensive treatment of chemoradiotherapy. Adelman and colleagues describe

risk factors for caregiver burden, which resemble our findings, such as female sex and cohabitation with the care recipient [11]. They describe caregivers who suffer from sleep deprivation are at higher risk, which seems to be in line with our finding that caregivers' baseline fatigue contribute to higher levels of burden after end of chemoradiotherapy. Longacre and colleagues describe in a review the psychological health of caregivers of patients with head and neck cancer [15]. They do not find a consistency on the caregivers' risk on higher levels of burden in relation to the female gender. The need for psychological help, however, is higher among women. Furthermore, they found a relation between treatment-related factors and caregiver burden. No association was found between caregiver distress and patient type of treatment and their functional impairment. They conclude that often no consistency is found in factors contributing to poorer mental health among caregivers, which could be a consequence of different methodology (small sample sizes and lack of longitudinal study design) and terminology (the definition of caregivers, for example).

This study adds valuable knowledge to the literature about the course of caregiver burden. The available data of caregivers' course of burden during and after treatment is limited and mostly regarding caregivers' burden during treatment. Nightingale and colleagues reported an increase in burden during radio- and/or chemotherapy, which remained high up to end of treatment [36]. Badr and colleagues reported constant levels of burden, up to 6 weeks after initiating treatment (radiotherapy alone, and / or in combination with prior surgery and / or chemotherapy) [6]. A recent pilot study of Nightingale and colleagues showed that caregivers of patients receiving radiotherapy, reported higher levels of burden during and one month after ending therapy [37]. Our study showed an increase in burden one week after chemoradiotherapy and a decrease to baseline levels three months after chemoradiotherapy. In order to prevent this rise in caregiver burden and the risk for burden after treatment, support for caregivers at risk for burden may be focused at the start of patient's treatment. Higher levels of burden and fatigue of the caregiver at the start of patients' treatment seem to contribute most to their burden after chemoradiotherapy. Based on this study, no conclusions can be drawn about determinants of baseline burden and fatigue and what kind of support for caregivers is needed. This should be determined with future research.

A main risk factor for caregivers' severe fatigue after patients finish chemoradiation is baseline fatigue. Fatigue is considered an important determinant for general health and levels of fatigue were higher among caregivers when compared to the general working population [38,39]. Additionally, fatigue severity was in the range of caregivers of patients in the palliative phase [33].

One could imagine that the intensive treatment with chemoradiotherapy, with daily visits to the hospital, and the impact of treatment-related side effects and their specific care demands may play an important role in caregivers' fatigue. Caregivers have to combine support for the patient with their own personal life. In this study, more than half of the caregivers combine their role as caregiver with work. It is known that being employed while caring for a significant other is challenging and can negatively influence caregivers' well-being, especially when caring demands flexibility while the caregivers' work demands otherwise [40]. Caregivers' fatigue, where a peak was found one week after chemoradiotherapy, is different from the constant levels reported by caregivers of patients in the palliative phase [33]. In order to support caregivers of patient with LAHNC coping with their own fatigue, it is important to know what causes fatigue before starting treatment. Our study shows that fatigue at baseline could be associated with patients' fatigue, distress and HRQoL. However, it remains unclear whether this causes caregivers' fatigue and therefore could be a focus for future research.

Although this study adds valuable knowledge, limitations should be considered. The predefined model for these exploratory analyses, based on clinical observations and supported by theory, contained a large number of predictors in a small sample size. Nevertheless, the exploratory model offers a direction for future studies with a larger sample size to identify caregivers at risk for burden and fatigue [41]. Furthermore, we may question the generalizability of our study for other LAHNC patients and their caregivers. Since the sample size is small, it is possible that our findings are too optimistic; the HRQoL of our sample in comparison to the reference group was significantly better at baseline. A possible explanation could be that the reference group represents stadium III and IV head and neck cancer patients, whereas our study only included patients with LAHNC without metastases (i.e. stages III, IVa, IVb). On the other hand, it is possible that our findings are more pessimistic; caregivers with lower levels of burden and patients with higher levels of HRQoL dropped out. An explanation for the latter could be that the caregivers with lower levels of burden and patients with higher levels of HRQoL, decided to withdraw from the study since they could not identify themselves with the purpose of the study.

In conclusion, burden of caregivers of LAHNC patients receiving chemoradiotherapy is determined by multiple variables and follows patients' peak in distress, fatigue and diminished HRQoL. Female, spousal caregivers who are burdened and fatigued at baseline are important to identify before a patient starts treatment in order to prevent burden after patients' ending of chemoradiotherapy. Where burden seems to be determined by multiple aspects, caregivers' fatigue after patients' curative treatment for LAHNC seems

predominantly caused by caregivers' fatigue at baseline. Fatigue is an important problem to identify, since it is an important determinant of a person's general health and ability to participate in society. Lastly, problems as a consequence of patients' treatment for LAHNC are likely to influence both the well-being of caregivers and patients. Therefore, it seems justified to involve both patients and caregivers when designing interventions addressing aforementioned issues.

REFERENCES

1. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363 (1):24-35. doi:10.1056/NEJMoa0912217
2. Argiris A, Karamouzis MV, Raben D, Ferris RL (2008) Head and neck cancer. Lancet 371 (9625):1695-1709. doi:10.1016/S0140-6736(08)60728-X
3. Bottomley A, Tridello G, Coens C, Rolland F, Tesselaar ME, Leemans CR, Hupperets P, Licitra L, Vermorken JB, Van Den Weyngaert D, Truc G, Barillot I, Lefebvre JL (2014) An international phase 3 trial in head and neck cancer: quality of life and symptom results: EORTC 24954 on behalf of the EORTC Head and Neck and the EORTC Radiation Oncology Group. Cancer 120 (3):390-398. doi:10.1002/cncr.28392
4. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, Kuik DJ, de Bree R, Leemans CR (2007) Distress in spouses and patients after treatment for head and neck cancer. The Laryngoscope 117 (2):238-241. doi:10.1097/01.mlg.0000250169.10241.58
5. Lydiatt WM, Moran J, Burke WJ (2009) A review of depression in the head and neck cancer patient. Clinical advances in hematology & oncology : H&O 7 (6):397-403
6. Badr H, Gupta V, Sikora A, Posner M (2014) Psychological distress in patients and caregivers over the course of radiotherapy for head and neck cancer. Oral oncology 50 (10):1005-1011. doi:10.1016/j.oraloncology.2014.07.003
7. Folkman S, Lazarus RS, Dunkel-Schetter C, DeLongis A, Gruen RJ (1986) Dynamics of a stressful encounter: cognitive appraisal, coping, and encounter outcomes. J Pers Soc Psychol 50 (5):992-1003
8. Pot AM, van Dyck R, Deeg DJ (1995) [Perceived stress caused by informal caregiving. Construction of a scale]. Tijdschrift voor gerontologie en geriatrie 26 (5):214-219
9. Nijboer C, Triemstra M, Tempelaar R, Sanderman R, van den Bos GA (1999) Determinants of caregiving experiences and mental health of partners of cancer patients. Cancer 86 (4):577-588
10. Zarit SH, Todd PA, Zarit JM (1986) Subjective burden of husbands and wives as caregivers: a longitudinal study. The Gerontologist 26 (3):260-266
11. Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS (2014) Caregiver burden: a clinical review. JAMA : the journal of the American Medical Association 311 (10):1052-1060. doi:10.1001/jama.2014.304
12. Haj Mohammad N, Walter AW, van Oijen MG, Hulshof MC, Bergman JJ, Anderegg MC, van Berge Henegouwen MI, Henselmans I, Sprangers MA, van Laarhoven HW (2015) Burden of spousal caregivers of stage II and III esophageal cancer survivors 3 years after treatment with curative intent. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer 23 (12):3589-3598. doi:10.1007/s00520-015-2727-4
13. Vickery LE, Latchford G, Hewison J, Bellew M, Feber T (2003) The impact of head and neck cancer and facial disfigurement on the quality of life of patients and their partners. Head & neck 25 (4):289-296. doi:10.1002/hed.10206
14. Ostroff J, Ross S, Steinglass P, Ronis-Tobin V, Singh B (2004) Interest in and barriers to participation in multiple family groups among head and neck cancer survivors and their primary family caregivers. Family process 43 (2):195-208

15. Longacre ML, Ridge JA, Burtness BA, Galloway TJ, Fang CY (2012) Psychological functioning of caregivers for head and neck cancer patients. Oral oncology 48 (1):18-25. doi:10.1016/j.oraloncology.2011.11.012
16. Stenberg U, Ruland CM, Miaskowski C (2010) Review of the literature on the effects of caring for a patient with cancer. Psycho-oncology 19 (10):1013-1025. doi:10.1002/pon.1670
17. Baghi M, Wagenblast J, Hambek M, Radeloff A, Gstoettner W, Scherzed A, Spaenkuch B, Yuan J, Hornung S, Strebhardt K, Knecht R (2007) Demands on caring relatives of head and neck cancer patients. The Laryngoscope 117 (4):712-716. doi:10.1097/mlg.0b013e318031d0b4
18. Romito F, Goldzweig G, Cormio C, Hagedoorn M, Andersen BL (2013) Informal caregiving for cancer patients. Cancer 119 Suppl 11:2160-2169. doi:10.1002/cncr.28057
19. Blood GW, Simpson KC, Dineen M, Kauffman SM, Raimondi SC (1994) Spouses of individuals with laryngeal cancer: caregiver strain and burden. Journal of communication disorders 27 (1):19-35
20. Nijboer C, Tempelaar R, Sanderman R, Triemstra M, Spruijt RJ, van den Bos GA (1998) Cancer and caregiving: the impact on the caregiver's health. Psycho-oncology 7 (1):3-13. doi:10.1002/(SICI)1099-1611(199801/02)7:1<3::AID-PON320>3.0.CO;2-5
21. Kim Y, Given BA (2008) Quality of life of family caregivers of cancer survivors: across the trajectory of the illness. Cancer 112 (11 Suppl):2556-2568. doi:10.1002/cncr.23449
22. Northouse LL, Mood D, Templin T, Mellon S, George T (2000) Couples' patterns of adjustment to colon cancer. Social science & medicine 50 (2):271-284
23. Kim Y, van Ryn M, Jensen RE, Griffin JM, Potosky A, Rowland J (2014) Effects of gender and depressive symptoms on quality of life among colorectal and lung cancer patients and their family caregivers. Psycho-oncology. doi:10.1002/pon.3580
24. Patterson JM, Rapley T, Carding PN, Wilson JA, McColl E (2013) Head and neck cancer and dysphagia; caring for carers. Psycho-oncology 22 (8):1815-1820. doi:10.1002/pon.3226
25. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta psychiatrica Scandinavica 67 (6):361-370
26. Vodermaier A, Millman RD (2011) Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 19 (12):1899-1908. doi:10.1007/s00520-011-1251-4
27. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM (1997) A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychological medicine 27 (2):363-370
28. Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, Ahlner-Elmqvist M, Maher EJ, Meyza JW, Bredart A, Soderholm AL, Arraras JJ, Feine JS, Abendstein H, Morton RP, Pignon T, Huguenin P, Bottomly A, Kaasa S (2000) A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. European journal of cancer 36 (14):1796-1807
29. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 16 (1):139-144
30. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G (1994) Dimensional assessment of chronic fatigue syndrome. Journal of psychosomatic research 38 (5):383-392

31. Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HWM, van Engelen BGM, van Riel P, Bleijenberg G, Nikolaus S, Knoop H (2017) The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. Journal of psychosomatic research 98:40-46. doi:10.1016/j.jpsychores.2017.05.007
32. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G (2013) Development of fatigue in cancer survivors: a prospective follow-up study from diagnosis into the year after treatment. J Pain Symptom Manage 45 (2):213-222. doi:10.1016/j.jpainsymman.2012.02.009
33. Peters ME, Goedendorp MM, Verhagen SA, Smilde TJ, Bleijenberg G, van der Graaf WT (2014) A prospective analysis on fatigue and experienced burden in informal caregivers of cancer patients during cancer treatment in the palliative phase. Acta oncologica:1-7. doi:10.3109/0284186X.2014.953254
34. Prinsen H, van Dijk JP, Zwarts MJ, Leer JW, Bleijenberg G, van Laarhoven HW (2015) The role of central and peripheral muscle fatigue in postcancer fatigue: a randomized controlled trial. J Pain Symptom Manage 49 (2):173-182. doi:10.1016/j.jpainsymman.2014.06.020
35. Scott NW FP, Bottomley A (2008) EORTC QLQ-C30 Reference Values Manual. EORTC Quality of Life Group publications: Brussels, Belgium. .
36. Nightingale CL, Lagorio L, Carnaby G (2014) A prospective pilot study of psychosocial functioning in head and neck cancer patient-caregiver dyads. J Psychosoc Oncol 32 (5):477-492. doi:10.1080/07347332.2014.936649
37. Nightingale CL, Curbow BA, Wingard JR, Pereira DB, Carnaby GD (2016) Burden, quality of life, and social support in caregivers of patients undergoing radiotherapy for head and neck cancer: A pilot study. Chronic illness 12 (3):236-245. doi:10.1177/1742395316644305
38. Northouse L, Williams AL, Given B, McCorkle R (2012) Psychosocial care for family caregivers of patients with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30 (11):1227-1234. doi:10.1200/JCO.2011.39.5798
39. Beurskens AJ, Bultmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM (2000) Fatigue among working people: validity of a questionnaire measure. Occupational and environmental medicine 57 (5):353-357
40. Swanberg JE (2006) Making it work: informal caregiving, cancer, and employment. J Psychosoc Oncol 24 (3):1-18. doi:10.1300/J077v24n03_01
41. Ogundimu EO, Altman DG, Collins GS (2016) Adequate sample size for developing prediction models is not simply related to events per variable. Journal of clinical epidemiology. doi:10.1016/j.jclinepi.2016.02.031

Chapter 3

Informal caregiver well-being during and after patients' treatment with adjuvant chemotherapy for colon cancer: a prospective, exploratory study

Simone M.C.H. Langenberg, Hanneke Poort, Anke N.M. Wymenga, Jan Willem de Groot, Erik W. Muller, Winette T.A. van der Graaf, Judith B. Prins, Carla M.L. van Herpen

Supportive Care in Cancer (2020) 29 (5): 2481-2491

ABSTRACT

Introduction: Caring for a significant other during cancer treatment can be demanding. Little is known about the well-being of informal caregivers of patients with colon cancer. This study aims to examine informal caregiver well-being during adjuvant chemotherapy for colon cancer.

Material and methods: This exploratory longitudinal, prospective study measured the course of informal caregiver burden (Self-Perceived Pressure of Informal Care), distress (Hospital Anxiety and Depression Scale), health-related quality of life (RAND-36), marital satisfaction (Maudsley Marital Questionnaire), social support (Social Support List – Discrepancies), fatigue (Abbreviated Fatigue Questionnaire), and self-esteem (Caregiver Reaction Assessment) before (T0), during (T1), and after (T2) patients' treatment.

Results: Baseline data of 60 out of 76 eligible dyads (79%) were analysed. Mean levels of informal caregiver burden and distress improved significantly over time, as did their health-related quality of life and perceived social support. At baseline, 30% and 26.7% of informal caregivers reported moderate-to-high levels of burden and clinically relevant levels of distress, respectively, which changed to 20% and 18.8% at T2. Informal caregiver burden and distress at baseline were the strongest predictors of informal caregiver burden and distress during and following patients' treatment, respectively.

Conclusion: When informal caregivers and patients experience problems before start of adjuvant chemotherapy, problems seem to improve over time. Approximately 20% of informal caregivers remain burdened and distressed after patients' end of treatment. Paying attention to baseline distress and burden seems indicated, as these were strong predictors of informal caregivers' wellbeing during and after treatment.

INTRODUCTION

Colon cancer is a common cancer among men and women [1]. In 2018, colon cancer accounted for 6% of all new cancer cases and 551,269 people died as a consequence of colon cancer worldwide [1]. In 2018, 9555 people were newly diagnosed with colon cancer in The Netherlands [2]. After diagnosis and staging, treatment plans are made according to (inter)national guidelines. When a patient is diagnosed with high-risk stage II or III colon cancer, surgical resection alone results in a 5-year survival rate of 60–80% for stage II and 30–60% for stage III disease [3]. To further improve survival, patients receive adjuvant chemotherapy containing fluoropyrimidines and oxaliplatin (i.e., 5FU/leucovorin with oxaliplatin (FOLFOX) or capecitabine with oxaliplatin (CAPOX)), or capecitabine monotherapy when oxaliplatin is contra-indicated [4, 5]. Common side effects of this regimen are nausea, vomiting, hand-foot syndrome, and sensory, peripheral neuropathy. Being diagnosed with cancer and receiving cancer treatment impact the patient and can cause psychological distress [6].

After a cancer diagnosis and during cancer treatment, support by a significant other is indispensable. Informal caregivers support patients both practically and emotionally [6, 7]. These tasks can cause burden and distress, which may impact an informal caregiver's ability to support the patient during treatment [8, 9]. Informal caregiver burden can be experienced on several dimensions and be related to emotional, social, physical, spiritual functioning, and/or practical and financial problems [7]. The National Cancer Institute defined distress as "emotional, social, spiritual or physical pain or suffering that may cause a person to feel sad, afraid, depressed, anxious or lonely" [10]. Previous studies identified burden and distress as important problems for informal caregivers [6, 9]. Patients and informal caregivers cope with cancer as a dyad and informal caregivers' distress may sometimes exceed patients' distress [11, 12]. Informal caregiver burden and distress are interrelated and share risk factors, such as female gender, younger age, and perceived patient distress [7, 9]. Importantly, informal caregiver burden and distress may also negatively influence the informal caregivers' physical health and social functioning [6–9]. Little is known about the course of well-being of informal caregivers of patients treated with adjuvant chemotherapy for colon cancer.

This prospective, observational study had four exploratory aims. First, we aimed to examine the course of informal caregiver well-being. Second, we intended to explore the clinically relevant levels of informal caregiver burden and distress. Third, we aimed to identify baseline risk factors for higher informal caregiver burden and distress during and after a patient's treatment. Fourth, we explored the association between informal caregiver burden and distress and patient distress before, during, and after adjuvant chemotherapy.

MATERIAL AND METHODS

Setting and participants

We conducted a prospective, observational study between October 2013 and September 2017 in four hospitals in The Netherlands. We recruited patients aged 18 or older, proficient in Dutch, who were scheduled to receive adjuvant chemotherapy (CAPOX or capecitabine monotherapy) after surgery for colon cancer, and their informal caregivers, for participation in this study.

Procedure

The attending physician or the nurse practitioner approached the patient and their informal caregiver for study participation after informing them about starting adjuvant chemotherapy. Written informed consents were obtained from both patient and informal caregiver. The study included completion of paper-and-pencil questionnaires at home at three time points: (1) baseline, before starting adjuvant chemotherapy (T0), (2) between the second and third cycle (T1), and (3) 3 months after ending adjuvant chemotherapy (T2). We asked patients and informal caregivers to complete questionnaires separately. The study was approved by the local medical ethics committee of the Radboud university medical center (registration number 2013/393).

Measures

Sociodemographic and clinical factors

Patients and informal caregivers self-reported their age, sex, level of education (categorized using the International Standard Classification of Education), and employment (paid work, housekeeper, disablement insurance act, retired, volunteer, study) at baseline. Informal caregivers completed a general questionnaire on the nature of their relation to the patient (partner, child, sibling, friend), whether they lived together with the patient (yes/no) and the extent of their caregiving tasks (hours of caring, independency of the patient, caring for more than patient alone), as well as their needs during caring for their significant other (practical and/or emotional support from social support system and/or professionals, information services from hospital and/or general practitioner, and/or better communication with physician/nurses/general practitioner). Furthermore, we inquired whether the treatment side effects of cancer treatment had a negative influence on informal caregiver well-being (no/ yes, somewhat/yes).

Patients self-reported whether they had a colostomy after surgery, the total number of cycles of adjuvant chemotherapy, and experienced toxicity (T1 and T2). Patients also reported what sort of complications they had after

surgery. The attending medical oncologist provided information which adjuvant chemotherapy (CAPOX versus capecitabine monotherapy) was prescribed.

We used the Self-administered Comorbidity Questionnaire (SCQ) to assess 14 common medical conditions in both patients and informal caregivers, and additional comorbidities could also be reported [13]. For each condition, patients and informal caregivers indicated whether it was present, being treated, or imposed functional limitations. For the present study, we used data on whether a comorbidity was present and causing functional limitations.

Informal caregiver well-being

Informal caregivers completed the 9-item Self-Perceived Pressure from Informal Care (SPPIC) [14]. Items are scored on a 5-point scale ranging from 0 (no!) to 5 (yes!). We dichotomized scores to 0 ("no!" and "no") and 1 ("yes!," "yes," and "more or less"). Total scores range from 0 to 9, and higher scores indicate higher levels of perceived informal caregiver burden. In accordance with other studies [15–17], we classified informal caregivers into low (0–3), moderate (4–6), and high levels of burden (7–9) based on their total score. Patients and informal caregivers each completed the Hospital Anxiety and Depression Scale (HADS) to measure distress [18].

The HADS consists of 14 items assessing symptoms of anxiety and depression during the past week. Items are scored on a 4-point Likert scale ranging from 0 to 3. Total scores range from 0 to 42, and higher scores indicate more distress. We used the 36-item RAND-36 Health Survey to assess functional status, well-being, and general health [19]. Scores on each of the eight subscales are transformed into a range from 0 to 100; higher scores indicate higher levels of functioning, well-being, and general health.

The Social Support List – Discrepancies (SSL-D) is a 34-item questionnaire assessing discrepancies between an individual's need for social support and their perceived social support [20, 21]. The questionnaire assesses six types of social support, namely emotional interactions, problem-focused emotional support, esteem support, instrumental interactions, social companionship, and informational support. The score on every item is transformed into a sum score ranging from 34 to 136. Higher scores indicate more unmet needs for social support.

We used the "marital satisfaction" subscale of the Maudsley Marital Questionnaire (MMQ) to assess marital satisfaction [22]. This is a 10-item questionnaire, answered on a 9-point scale (0–8), ranging from 0 to 80. Higher scores indicate decreased marital satisfaction. We instructed participants to complete this questionnaire if they had a partner relationship.

We administered the Abbreviated Fatigue Questionnaire (AFQ), a validated 4-item questionnaire to measure fatigue [23, 24]. The AFQ is an abbreviated version of the subscale fatigue severity of the Checklist Individual Strength. Items are scored on a 7-point scale ranging from "no, that's not correct" (score 1) to "yes, that's correct" (score 7). The total score on the 4-item questionnaire ranges from 4 to 28. Higher scores indicate greater levels of fatigue.

Informal caregiver self-esteem was measured by the subscale caregiver self-esteem of the Caregiver Reaction Assessment Scale (CRA) [25]. The subscale consists of 7 items, scored on a 5-point Likert scale. The total score reflects a mean score of 7 items and ranges between 1 and 5; a higher score indicates more self-esteem.

Statistical analysis

Descriptive statistics were used for baseline characteristics of the patients and informal caregivers. Chi-square and Fisher's exact tests were performed to examine the relation between categorical variables. Independent-samples t tests and Mann-Whitney U tests were used to compare continuous variables. We analysed informal caregiver burden, distress, health-related quality of life, marital satisfaction, discrepancies in social needs, fatigue, and informal caregiver self-esteem with one-way ANOVA with repeated measure. Next, we applied the same statistical analyses for patient distress, health-related quality of life, marital satisfaction, discrepancies in social needs, and fatigue. We applied the Greenhouse-Geisser correction when the assumption of sphericity was violated. Post hoc tests with Bonferroni's correction were used to identify which specific means differed. To identify cases of clinically significant distress, we applied a HADS total clinical cutoff score of ≥ 11 to identify patients with clinically significant distress [26] and a cutoff score of ≥ 12 for informal caregivers [27]. To identify possible cases of depression (HADS-D) and anxiety (HADS-A), we used the cutoff score of ≥ 8 [26, 27]. McNemar's tests were carried out to determine whether the proportion of patients or informal caregivers exceeding the cutoff for clinically relevant distress differed between baseline and T2. We used multiple linear regression to predict informal caregiver burden and distress at T1 and T2 from informal caregiver gender, age, burden, distress, fatigue, and patient distress at baseline (method: enter). For the linear regression analyses, we used the continuous variables of burden, distress, and fatigue. All data analyses were performed using the statistical package for the social sciences (SPSS, version 24.0). Statistical significance was determined based on a two-sided alpha of 0.05.

RESULTS

Of 76 eligible patients and their informal caregivers, 62 (82%) dyads enrolled in the study, and 14 (18%) declined participation, mostly because participation was considered too burdensome. Of the 62 dyads that provided consent, 2 dyads withdrew consent after enrollment. Thus, T0 was completed by 60 (79%), whereas T1 by 58 (76%) and T2 by 51 dyads (67%). Baseline, caregiving, and treatment characteristics are provided in Table 1. Table 2 displays an overview of what support informal caregivers need before, during, and after a patients' treatment with adjuvant chemotherapy. When informal caregivers reported they need support, it seemed most needed before starting chemotherapy and focused on practical support and receiving information.

Table 1. Characteristics of informal caregivers and patients

	Informal Caregivers (n=60)	Patients (n=60)
Age, years (SD)	59.88 (12.72)	63.83 (7.74)
Sex		
Male	25 (41.7%)	34 (56.7%)
Female	35 (58.3%)	26 (43.3%)
Education		
Lower education level (ISCED ≤ 4)	35 (58.3%)	41 (69.5%)
Higher education level (ISCED 5-8)	25 (41.6%)	18 (30.5%)
Missing	0	1
Dependent children (lives with)		
No	43 (71.7%)	
Yes	9 (15.0%)	
Missing	8 (13.3%)	
Employment [a]		
Paid work	23 (38.3%)	19 (31.7%)
Housekeeper	9 (15%)	7 (11.7%)
Disablement insurance act	0 (0%)	7 (11.7%)
Retired	25 (41.7%)	28 (46.7%)
Volunteer work	4 (6.7%)	3 (5%)
Study	2 (3.3%)	0 (0%)
Informal caregiver's relationship to patient		
Partner	53 (91.4%)	
Child	2 (3.4%)	
Sibling	2 (3.4%)	
Friend	1 (0.8%)	
Missing	2	

Table 1. Continued

	Informal Caregivers (n=60)	Patients (n=60)
Informal caregiver lives with patient		
Yes	53 (89.8%)	
No	6 (10.2%)	
Missing	1	
Providing > 8 hours of care		
T0	19/60 (31.9%)	
T1	18/57 (31.6%)	
T2	5/51 (9.9%)	
Patients functioned independently or mostly independently		
T0	51/57 (89.5%)	
T1	51/57 (89.5%)	
T2	48/51 (94.2%)	
Providing care to more than patient alone		
T0	7/60 (11.9%)	
T1	5/57 (8.8%)	
T2	3/51 (5.9%)	
Negative influence of patients' side effects on caregiver well-being (measured on T1)		
No	22/53 (41.5%)	
Yes, somewhat	27/53 (50.9%)	
Yes	4/53 (7.5%)	
Colostomy after surgery		
No		52 (86.7%)
Yes		8 (13.3%)
Complications after surgery [a]		
No		28 (46.7%)
Obstipation		8 (13.4%)
Wound leakage/infection		8 (13.4%)
Anastomotic leakage		3 (5.0%)
Bleeding / anaemia		2 (3.4%)
Thrombosis		1 (1.7%)
High blood pressure		1 (1.7%)
Urinary catheter		1 (1.7%)
Urinary tract infection		1 (1.7%)
Gastroparesis		2 (3.4%)
Ileus		1 (1.7%)
Cardiac arrest		1 (1.7%)
Stoma retraction		1 (1.7%)

Table 1. Continued

	Informal Caregivers (n=60)	Patients (n=60)
Type of adjuvant chemotherapy		
CAPOX		53 (88.3%)
Capecitabine monotherapy		7 (11.7%)
Number of cycles completed		
8		37 (72.5%)
7		6 (7.8%)
6		4 (7.8%)
5		1 (2%)
4		1 (2%)
3		1 (2%)
2		1 (2%)
1		0 (0%)
Missing		9
Reason for modification treatment (n=26)		
Discontinuation oxaliplatin only		13/26 (50%)
Discontinuation oxaliplatin and capecitabine		13/26 (50%)
Toxicity 3 months after ending adjuvant treatment		
No		1 (2%)
Yes, suffered from side effect, but disappeared		15 (29.4%)
Yes, suffered from side effects, now barely noticeable		4 (7.8%)
Yes, suffered from side effects and still do		31 (60.8%)
Missing		9
Comorbidities		
0	16 (29.1%)	11 (20.0%)
1-2	34 (61.8%)	35 (63.7%)
3 or more	5 (9.1%)	9 (16.4%)
Missing	5	5
Most common comorbidities		
High blood pressure	15/59 (25.4%)	22/58 (37.9%)
Back pain	15/57 (26.3%)	14/58 (24.1%)
Arthrosis	12/57 (21.1%)	8/58 (13.8%)
Chronic obstructive pulmonary disease	10/57 (17.5%)	7/57 (16.7%)
Diabetes	6/58 (10.3%)	10/58 (17.2%)
Hearth disease	2/57 (3.5%)	11/58 (19%)

Table 1. Continued

	Informal Caregivers (n=60)	Patients (n=60)
Hindrance from comorbidit(y)(ies)		
High blood pressure	1/15 (6.7%)	0/22 (0%)
Back pain	7/15 (46.7%)	6/12 (50%)[c]
Arthrosis	6/11 (54.5%)[b]	1/8 (12.5%)
Chronic obstructive pulmonary disease	5/10 (50%)	1/6 (16.7%)[b]
Diabetes	1/6 (16.7%)	1/9 (11.1%)[b]
Heath disease	0/2 (0%)	2/9 (18.2%)[c]

SD = standard deviation; ISCED = International Standard Classification of Education 2011; ≤ 4: secondary, non-tertiary education level, > 4: tertiary education level (bachelor, master or doctoral level); T0 = baseline, T1 = between 2nd and 3rd cycle of adjuvant chemotherapy, T2 = 3 months after ending adjuvant chemotherapy; CAPOX = capecitabine with oxaliplatin

[a] Multiple answers possible; [b] One missing answer; [c] Two missing answers

Table 2. Informal caregivers' needs for support before, during and after adjuvant chemotherapy

	Baseline (n=60)	After second Tx cycle (n=57)	Three months after completing Tx (n=51)
No support needed	39 (65.0%)	43 (75.4%)	42 (82.4%)
Practical support			
From social support system	5	3	1
From professional	8	4	4
Emotional support			
From social support system	1	0	1
From professional	2	1	2
Information services			
From hospital	6	2	1
From general practitioner	3	1	2
Better communication			
With physician	1	1	2
With nurses	0	1	1
With general practitioner	1	2	1
Other	3	2	1

Course of burden, distress, health-related quality of life, marital satisfaction, discrepancies in social needs, fatigue over time, and informal caregiver self-esteem.

Table 3 shows mean scores for informal caregiver well-being over time. Mean scores for informal caregiver burden ($F[2,94] = 4.465$; $p=0.014$), distress ($F[1.773,81.574] = 5.497$; $p=0.008$), role emotional limitations ($F[2,94] = 8.814$; $p<0.0001$), mental health ($F[2,94] = 4.949$; $p=0.009$), social functioning ($F[2,98] = 3.985$; $p=0.022$), and discrepancies in social support ($F[2,66] = 3.466$; $p=0.037$) differed significantly between time points. Post hoc analyses indicated an improvement of all scores over time; i.e., burden, distress, and role emotional limitations decreased, whereas mental health and social functioning increased. Discrepancies in social support decreased during and increased after ending adjuvant chemotherapy. Post hoc analyses are shown in Table 4.

Table 5 displays patients' mean scores for health-related quality of life, marital satisfaction, discrepancies in social needs, and fatigue over time. Mean patient distress ($F[1.771,79.706] = 5.224$; $p=0.010$), role physical limitations ($F[2,94] = 9.551$; $p<0.0001$), vitality ($F[2,96] = 5.295$; $p=0.007$), social functioning ($F[2,96] = 9.157$; $p<0.0001$), general health ($F[2,92] = 6.672$; $p=0.002$), marital satisfaction ($F[2,54] = 5.395$; $p=0.007$), and fatigue ($F[2,92] = 11.393$; $p<0.0001$) changed significantly over time. Post hoc analyses revealed an overall decrease of distress and increase in role physical limitations and social functioning. Vitality and general health decreased during and increased after ending adjuvant chemotherapy. Marital satisfaction decreased over time. Fatigue increased during and decreased after ending adjuvant chemotherapy. Post hoc analyses are shown in Table 6.

Clinically relevant levels of informal caregiver burden and distress

Moderate or high levels of burden of informal caregivers were found in 17.2% (n=10/58) and 12.1% (n=7/58) at baseline, 19.3% (n=11/57) and 10.5% (n=6/57) at T1, and 12% (n=6/50) and 8% (n=4/50) at T2, respectively. A HADS total score exceeding the cutoff for clinically relevant distress was found in 26.7% (n=16/60) at baseline, 22.8% (n=13/57) at T1, and 18.8% (n=9/48) at T2. Clinically relevant levels of informal caregiver depressive symptoms (HADS-D) were 15% at baseline, 10.5% at T1, and 12.2% at T2. Clinically relevant levels of informal caregiver anxiety (HADS-A) were 21.7% at baseline, 21.1% at T1, and 12.2% at T2.

Table 3. Informal caregivers' course of burden, distress, health-related quality of life, marital satisfaction, fatigue and self-esteem

	Population norm scores
	Mean (SD)
Burden (SPPIC) [14,15]	[a]
Distress (HADS) [27]	8.4 (6.3)
Health-related quality of life (RAND 36) [19]	
Physical functioning	81.90 (23.20)
Role limitations due to physical health	79.40 (35.50)
Role limitations due to emotional problems	84.10 (32.30)
Vitality	67.40 (19.90)
Mental health	76.80 (18.40)
Social functioning	86.90 (20.50)
Pain	79.50 (25.60)
General health	72.70 (22.70)
Marital satisfaction (MMQ) [22,38]	13.58 (10.79)
Social support discrepancies (SSL-D) [21]	43.6 (10.3)
Fatigue (AFQ) [24]	[b]
Self Esteem (CRA) [39]	4.19 (0.41)

SPPIC = Self-Perceived Pressure of Informal Care, HADS = Hospital Anxiety and Depression Scale, MMQ = Maudsley Marital questionnaire, SSL-D = Social Support List – Discrepancies, AFQ = Abbreviated Fatigue Questionnaire, CRA = Caregiver Reaction Assessment; T0 = baseline, T1 = between 2nd and 3rd cycle of adjuvant chemotherapy,

Table 4. Post-hoc analyses of courses of informal caregiver variables which differed significantly

Measure	**Burden**				**Distress**				**Role emotional limitations**			
	Δ	95% CI		Sign	Δ	95% CI		Sign	Δ	95% CI		Sign
		Lower bound	Upper bound			Lower bound	Upper bound			Lower bound	Upper bound	
T2 versus T1	-0.085	-0.942	0.771	1.000	-1.383	-2.899	0.133	.085	17.361	1.975	32.747	.022*
T3 versus T1	-0.862	-1.642	-0.099	.022*	-2.319	-4.349	-0.290	.020*	22.222	7.784	36.660	.001*
T3 versus T2	-0.777	-1.521	-0.033	.038*	-0.936	-2.596	0.724	.503	4.861	-6.428	16.150	.871

Δ = mean difference; CI = confidence interval; T0=before starting adjuvant chemotherapy; T1=between 2nd and 3rd cycle; T2=three months after ending chemotherapy; sign.= significance; *significant mean difference

T0	**T1**	**T2**	**Sign**
Mean (SD)	*Mean (SD)*	*Mean (SD)*	*p-value*
2.90 (2.44)	2.82 (2.38)	2.04 (2.25)	0.014*
8.96 (6.91)	7.57 (6.32)	6.64 (7.15)	0.008*
91.04 (10.47)	90.94 (13.90)	87.81 (16.24)	0.153
79.89 (23.20)	87.50 (22.82)	84.78 (30.95)	0.253
63.88 (41.73)	81.25 (34.32)	86.11 (30.62)	<0.0001*
67.29 (14.73)	71.98 (15.04)	71.88 (20.39)	0.067
73.00 (14.16)	77.08 (12.83)	78.33 (14.41)	0.015*
80.00 (20.52)	84.75 (18.09)	87.00 (15.14)	0.022*
92.00 (12.98)	89.63 (15.63)	88.30 (17.17)	0.173
74.56 (16.68)	75.56 (16.42)	73.33 (20.83)	0.430
9.76 (9.94)	10.37 (10.80)	11.66 (11.53)	0.189
41.18 (9.09)	38.38 (5.68)	39.06 (6.63)	0.037*
10.02 (2.65)	10.49 (6.30)	10.55 (7.26)	0.748
4.32 (0.54)	4.32 (0.49)	4.23 (0.48)	0.181

T2 = 3 months after ending adjuvant chemotherapy; * p-values represent significant changes in mean scores over time; references given in this table refer to population norm scores; [a] Scores for levels of burden: 0-3 low, 4-6 moderate, 7-9 high; [b] Scores for level of fatigue: low = 4, below average = 4, average = 5-8, above average = 9-14, high ≥ 15

	Mental health				**Social functioning**				**Social support discrepancies**			
Δ	95% CI		Sign	Δ	95% CI		Sign	Δ	95% CI		Sign
	Lower bound	Upper bound			Lower bound	Upper bound			Lower bound	Upper bound	
4.083	-0.327	8.494	.078	4.750	-0.980	10.480	.136	2.794	-5.629	0.041	.054
5.333	0.058	10.609	.047*	7	0.190	13.810	.042*	-2.118	-4.803	0.567	.165
1.250	-2.045	4.545	1.000	2.250	-3.991	8.491	1.000	0.676	-2.178	3.531	1.000

Table 5. Patient course of distress, health-related quality of life, marital satisfaction, fatigue and self-esteem

	Population norm scores
	Mean (SD)
Distress (HADS) [27]	8.4 (6.3)
Health-related quality of life (RAND 36) [19]	
Physical functioning	81.90 (23.20)
Role limitations due to physical health	79.40 (35.50)
Role limitations due to emotional problems	84.10 (32.30)
Vitality	67.40 (19.90)
Mental health	76.80 (18.40)
Social functioning	86.90 (20.50)
Pain	79.50 (25.60)
General health	72.70 (22.70)
Marital satisfaction (MMQ) [38]	13.58 (10.79)
Social support discrepancies (SSL-D) [21]	43.2 (10.7)
Fatigue (AFQ) [24]	[a]

HADS = Hospital Anxiety and Depression Scale, MMQ = Maudsley Marital questionnaire, SSL-D = Social Support List – Discrepancies, AFQ = Abbreviated Fatigue Questionnaire; T0 = baseline, T1 = between 2nd and 3rd cycle of adjuvant chemotherapy,

Table 6. Post-hoc analyses of courses of patient variables which differed significantly

Patient		**Distress**				**Role physical limitations**				**Vitality**		
Measure	Δ	95% CI		Sign	Δ	95% CI		Sign	Δ	95% CI		Sign
		Lower bound	Upper bound			Lower bound	Upper bound			Lower bound	Upper bound	
T2 versus T1	0.152	1.473	1.777	1.000	1.563	-16.955	20.080	1.000	-6.429	-12.227	-0.630	.025*
T3 versus T1	-1.674	-3.423	0.075	.065	27.604	12.563	42.645	<.0001*	0.306	-5.220	5.832	1.000
T3 versus T2	-1.826	-3.087	-0.565	.002*	26.042	7.019	45.065	.004*	6.735	0.676	12.793	.025*

Δ = mean difference; CI = confidence interval; T0=before starting adjuvant chemotherapy; T1=between 2nd and 3rd cycle; T2=three months after ending chemotherapy; sign.= significance; *significant mean difference

T0	**T1**	**T2**	**Significant difference over time**
Mean (SD)	*Mean (SD)*	*Mean (SD)*	*p-value*
7.22 (6.04)	7.37 (5.41)	5.54 (4.31)	0.010*
76.35 (19.76)	76.15 (20.78)	79.52 (20.85)	0.168
31.77 (40.52)	33.33 (38.71)	59.36 (45.44)	<0.0001*
65.93 (44.66)	74.81 (40.92)	85.19 (33.75)	0.061
64.59 (17.61)	58.16 (18.33)	64.90 (19.59)	0.007*
79.92 (14.64)	70.49 (14.33)	82.45 (11.07)	0.344
68.37 (19.45)	72.45 (20.41)	82.14 (19.76)	<0.0001*
74.90 (23.06)	74.82 (22.63)	80.42 (20.56)	0.285
63.51 (19.33)	60.00 (18.44)	68.62 (20.50)	0.002*
5.79 (6.85)	6.86 (8.37)	9.00 (9.58)	0.007*
36.86 (4.90)	36.19 (3.03)	36.06 (3.18)	0.445
12.36 (6.61)	16.21 (7.23)	12.85 (6.37)	<0.0001*

T2 = 3 months after ending adjuvant chemotherapy; * p-values represent changes in mean scores over time; references given in this table refer to population norm scores; [a] Scores for level of fatigue: low = 4, below average = 5-12, average = 13-21, above average = 22-27, high ≥ 28

	Social functioning				**General health**				**Marital satisfaction**				**Fatigue**			
Δ	95% CI		Sign	Δ	95% CI		Sign	Δ	95% CI		Sign	Δ	95% CI		Sign	
	Lower bound	Upper bound			Lower bound	Upper bound			Lower bound	Upper bound			Lower bound	Upper bound		
4.082	-5.245	13.409	.849	-3.511	-8.551	1.529	.271	1.071	-1.141	3.284	.681	3.851	1.722	5.980	<.0001*	
13.776	6.090	21.461	<.0001*	5.106	-0.802	11.015	.111	3.214	0.370	6.059	.023*	0.489	-1.606	2.585	1.000	
9.694	2.223	17.165	.007*	8.617	1.989	15.245	.007*	2.143	-0.392	4.677	.120	-3.362	-5.678	-1.045	.002*	

In patients, 22.4% (n=13/58) exceeded the cutoff at baseline for clinically relevant levels of distress, 31.5% (n=17/54) at T1, and 18.0% (n=9/50) at T2. Clinically relevant levels of patient depression were 12.1% at baseline, 16.1% at T1, and 7.8% at T2. Clinically relevant levels of patient anxiety were 17.2% at baseline, 13.0% at T1, and 7.8% at T2. There was no significant difference between the proportions of informal caregivers (p=0.289) or patients (p=0.508) with clinically relevant levels of distress at baseline and T2.

Predictors of informal caregiver distress and burden at T1 and T2

Informal caregiver gender, age, burden, distress, fatigue, and patient distress at baseline predicted informal caregiver self-perceived burden at T1 ($F[6,53] = 4.493$, $p=0.001$, $R^2 = 0.365$) and T2 ($F[6,46] = 4.523$, $p<0.001$, $R^2 = 0.404$). Only informal caregiver burden at baseline added significantly to the prediction at T1 (p=0.002) and T2 (p=0.002). The multivariate regression model was also used to predict distress at T1 ($F[6,53] = 12.305$, $p<0.0001$, $R^2 = 0.611$) and T2 ($F[6,44] = 7.204$, $p<0.0001$, $R^2 = 0.532$). Only baseline informal caregiver distress (p<0.001) added significantly to the prediction at T1 (p<0.001) and T2 (p=0.001). Details are displayed in Table 7.

Table 7. Multivariate regression analyses to explore associations with informal caregiver burden and distress during and after patients' treatment with adjuvant chemotherapy

	Burden T1		**Burden T2**		**Distress T1**		**Distress T2**	
Informal caregiver characteristics	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Age	0.021	0.862	-0.134	0.290	-0.028	0.761	-0.066	0.876
Gender	-0.082	0.497	-0.032	0.799	-0.008	0.931	0.042	0.819
Burden T0	0.440	0.002*	0.478	0.002*	-0.011	0.917	0.002	0.988
Distress T0	0.294	0.065	0.100	0.533	0.716	0.000*	0.544	0.001*
Fatigue T0	-0.056	0.720	0.115	0.472	0.119	0.335	0.275	0.063
Patient characteristics								
Distress T0	0.014	0.909	0.037	0.777	-0.110	0.258	-0.105	0.395
R^2	37%		40%		61%		53%	

* Statistically significant

Interaction between informal caregivers and patients

Generally, informal caregivers reported higher distress levels (T0 mean 8.47 (SD=6.83); T1 M=7.42 (SD=6.34); T2 M=6.50 (SD=7.14)) compared with patients (T0 M=7.02 (SD 5.80); T1 M=7.20 (SD=5.93); T2 M=5.56 (SD=4.69)), but these differences did not reach statistical significance (T0 mean difference 1.45, p=0.217; T1 mean difference 0.22,

p=0.853; T2 mean difference 0.94, p=0.445). We did not find significant correlations between informal caregiver and patient distress at baseline (r=0.134, p=0.315), T1 (r=0.263, p=0.054), or T2 (r=0.121, p=0.424). In addition, informal caregiver burden and patient distress did not correlate significantly at T1 (r=0.209, p=0.129) or T2 (r=0.205, p=0.167). However, at baseline, informal caregiver burden was significantly, but weakly correlated with patient distress (r=0.261, p=0.05).

DISCUSSION

The present longitudinal study explored the course of informal caregiver well-being, clinically relevant levels of informal caregiver burden and distress, and baseline risk factors for higher levels of burden and distress during and after a patients' adjuvant chemotherapy for colon cancer. We found that informal caregivers seem to report more mental problems before and during chemotherapy, whereas patients report more physical problems. Additionally, 20–30% of informal caregivers report relevant levels of burden and distress, between, before, during, and after a patients' treatment. Baseline burden and distress are risk factors for burden and distress during and after a patients' adjuvant treatment.

Informal caregivers reported more mental than physical problems after a patient's cancer diagnosis and during treatment, and social functioning seemed to be influenced negatively. This was also found in another study on the impact of colorectal cancer on patients and their partners [30]. This study of Traa et al. showed that both partners and patients suffer mentally and in social functioning, which is in line with our findings. Furthermore, a study of Law et al. showed that informal caregivers' social functioning changed due to fear of burdening others, and when informal caregivers do get support, this support is perceived insufficient and not what they need on that moment [31]. Also, informal caregivers report that family and friends become avoidant in their contact with the patient and informal caregiver, which challenges their social interactions [32]. In contrast to the findings of Traa et al. who found a stabilization in mental well-being and social functioning, we observed an improvement over time. A possible explanation could be that in the study of Traa et al., 60% had an colostomy after surgery compared with only 13% in our study. Having a colostomy is known to cause distress for the patient and their informal caregiver and may impact social activities and increase social isolation [32–35].

Before starting adjuvant chemotherapy, almost 30% of informal caregivers reported moderate-to-high levels of burden and clinically relevant distress, which decreased to 20% 3 months after the end of adjuvant treatment. Ohlsson-Nevo et al. pointed out that partners' lives are turned upside down after colorectal

cancer diagnosis, being confronted with how fragile life is [33]. They had to deal with new and other unwanted responsibilities at home that they felt compelled to fulfill [33]. Northouse et al. found that during patients' treatment for cancer, informal caregivers experienced worries about the effectiveness of the treatment, accompanied by difficulties managing side effects [6]. For informal caregivers who still experienced burden and distress after the patient's completion of adjuvant chemotherapy, a possible contributing factor could be the ongoing treatment toxicity, which was reported by 61% of the patients in our study. Although toxicity can diminish over time, there is a group of patients for which the toxicity, in particular peripheral neuropathy, remains a limiting factor in a patients' life [36], and thereby also influences the life of their significant others. Fortunately, there are new insights for treating stage III colon cancer, namely a shift from 6 to 3 months CAPOX, which is non-inferior in terms of survival and induces less toxicity [36]. Our study was performed when these data were not available yet. Since the number of cycles will be reduced and thereby also the associated cumulative toxicity, this may ultimately also positively impact the informal caregiver [36]. Another contributing factor for ongoing burden and distress can be fear of cancer recurrence. This is found in patients, and van de Wal et al. found that partners report the same levels of fear of recurrence as well. [37]

When thinking of ways to support informal caregivers in need, it could be particularly helpful to predict who is in need of support and when. In our study, we found that informal caregiver burden and distress at baseline predicted informal caregiver burden and distress both during adjuvant chemotherapy and 3 months after completion of treatment. Jansen et al. reported that informal caregivers of patients with different types of cancer with higher baseline levels of burden remained burdened over the following years [38]. It is possible that informal caregivers who remain burdened and distressed have more difficulties coping, as negative coping skills are associated with higher levels of burden and distress [39]. Further research with ongoing assessment of burden and distress due to the dynamic nature of these constructs, with a focus on what causes and maintains burden and distress, is recommended. Especially it is known that long-term burden and distress cause serious general health problems [7]. Additionally, our study shows that informal caregivers' distress exceeds patients' distress. This finding is consistent with those of other studies [6, 30]. Based on these findings, we recommend to pay attention and offer support when informal caregiver burden and distress are observed before starting adjuvant chemotherapy, or even earlier, shortly after diagnosis. More specifically, repeated assessment of informal caregiver needs for more practical support or other informational services from care professionals is recommended. Importantly, the management of treatment side effects deserves special attention

as 60% of informal caregivers report that their well-being is negatively influenced by patients' side effects during treatment. Additionally, based on our inquiry of informal caregiver needs, the general practitioner may be particularly well-suited for providing support to the informal caregiver, as leading practitioner in informal caregiver care.

Our exploratory longitudinal study adds significantly to the scarce literature on informal caregiver burden and distress during adjuvant treatment of colon cancer. However, it is important to take into account several limitations. First, the sample size is relatively small which prevented us from studying additional predictors of informal caregiver burden and distress, such as the influence of a patient's colostomy. Second, patients and informal caregivers who declined participation in this study often refused because participation was perceived too burdensome. This may limit the generalizability of our findings and our conclusion on burden and distress to the larger population of informal caregivers, and our findings may be an underestimation. Third, although we assessed statistical significance of changes in informal caregiver wellbeing over time, we were unable to determine clinical relevance due to the lack of established minimally clinically important differences (MCID) for the measures that we used. Future research assessing MCIDs for among informal caregiver population is warranted.

In conclusion, before and during adjuvant chemotherapy, informal caregivers report more mental problems whereas patients report more physical problems. When informal caregivers and patients experience problems before start of adjuvant chemotherapy, problems seem to improve over time. Nevertheless, approximately 20% of informal caregivers remain burdened and distressed after patients' end of treatment, and remarkably informal caregivers' distress exceeds patients' distress. Additionally, informal caregivers' baseline burden and distress seem to be risk factors for ongoing burden and distress after treatment. Therefore, it is of great importance to identify burden and distress among informal caregivers of patients treated with adjuvant chemotherapy for colon cancer and offer them support according to their needs.

REFERENCES

1. Union for International Cancer Control - GLOBOCAN (2018) https://www.uicc.org/news/new-global-cancer-data-globocan-2018
2. Incidentie darmkanker www.cijfersoverkanker.nl
3. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A, Arnold D, Group EGW (2013) Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24 (Suppl 6):vi64–vi72. https://doi.org/10. 1093/annonc/mdt354
4. Shah MA, Renfro LA, Allegra CJ, Andre T, de Gramont A, Schmoll HJ, Haller DG, Alberts SR, Yothers G, Sargent DJ (2016) Impact of patient factors on recurrence risk and time dependency of oxaliplatin benefit in patients with colon cancer: analysis from modern-era adjuvant studies in the Adjuvant Colon Cancer End Points (ACCENT) database. J Clin Oncol 34(8):843–853. https://doi.org/10.1200/JCO.2015.63.0558
5. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27(19):3109–3116. https://doi. org/10.1200/JCO.2008.20.6771
6. Northouse LL, Katapodi MC, Schafenacker AM, Weiss D (2012) The impact of caregiving on the psychological well-being of family caregivers and cancer patients. Semin Oncol Nurs 28(4):236–245. https://doi.org/10.1016/j.soncn.2012.09.006
7. Northouse L, Williams AL, Given B, McCorkle R (2012) Psychosocial care for family caregivers of patients with cancer. J Clin Oncol 30(11):1227–1234. https://doi.org/10.1200/JCO.2011. 39.5798
8. Applebaum AJ, BreitbartW(2012) Care for the cancer caregiver: a systematic review. Palliat Support Care 11:1–22. https://doi.org/10. 1017/S1478951512000594
9. Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS (2014) Caregiver burden: a clinical review. JAMA 311(10):1052–1060. https://doi.org/10.1001/jama.2014.304
10. National Cancer Institute - definition of distress. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/distress
11. Kim Y, van Ryn M, Jensen RE, Griffin JM, Potosky A, Rowland J (2014) Effects of gender and depressive symptoms on quality of life among colorectal and lung cancer patients and their family caregivers. Psycho-oncology. 24:95–105. https://doi.org/10.1002/pon. 3580
12. Northouse LL, Mood D, Templin T, Mellon S, George T (2000) Couples' patterns of adjustment to colon cancer. Soc Sci Med 50(2):271–284
13. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN (2003) The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 49(2):156–163. https://doi.org/10.1002/art.10993
14. Pot AM, van Dyck R, Deeg DJ (1995) Perceived stress caused by informal caregiving. Construction of a scale. Tijdschr Gerontol Geriatr 26(5):214–219
15. Haj Mohammad N, Walter AW, van Oijen MG, Hulshof MC, Bergman JJ, Anderegg MC, van Berge Henegouwen MI, Henselmans I, Sprangers MA, van Laarhoven HW (2015) Burden of spousal caregivers of stage II and III esophageal cancer survivors 3 years after treatment with curative intent. Support Care Cancer 23(12):3589–3598. https://doi.org/10.1007/s00520-015-2727-4

16. Langenberg S, Reyners AKL, Wymenga ANM, Sieling GCM, Veldhoven CMM, van Herpen CML, Prins JB, van der Graaf WTA (2019) Caregivers of patients receiving long-term treatment with a tyrosine kinase inhibitor (TKI) for gastrointestinal stromal tumour (GIST): a cross-sectional assessment of their distress and burden. Acta Oncol 58(2):191–199. https://doi.org/10.1080/0284186X.2018.1518592
17. Langenberg S, van Herpen CML, van Opstal CCM, Wymenga ANM, van der Graaf WTA, Prins JB (2019) Caregivers' burden and fatigue during and after patients' treatment with concomitant chemoradiotherapy for locally advanced head and neck cancer: a prospective, observational pilot study. Support Care Cancer 27(11): 4145–4154. https://doi.org/10.1007/s00520-019-04700-9
18. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370
19. VanderZee KI, Sanderman R, Heyink JW, de Haes H (1996) Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 3(2):104–122. https://doi.org/10.1207/s15327558ijbm0302_2
20. Bridges KR, Sanderman R, van Sonderen E (2002) An English language version of the social support list: preliminary reliability. Psychol Rep 90(3 Pt 1):1055–1058. https://doi.org/10.2466/pr0.2002.90.3.1055
21. VanSonderen E (2012) Het meten van sociale steun met de Sociale Steun Lijst - Interacties (SSL-I) en Sociale Steun Lijst - Discrepanties (SSL-D): een handleiding. Tweede herziene druk
22. Arrindell WA, Schaap C (1985) The Maudsley Marital Questionnaire (MMQ): an extension of its construct validity. Br J Psychiatry 147:295–299
23. Bleijenberg G, KnoopH,GielissenM(2009) ['Abbreviated Fatigue Questionniare to establish the severity of chronic fatigue'] Bijblijven (Tijdschrift Praktische Huisartsgeneeskunde) (1):19–21
24. Alberts M, Smets EM, Vercoulen JH, Garssen B, Bleijenberg G (1997) 'Abbreviated fatigue questionnaire': a practical tool in the classification of fatigue. Ned Tijdschr Geneeskd 141(31):1526–1530
25. Given CW, Given B, Stommel M, Collins C, King S, Franklin S (1992) The caregiver reaction assessment (CRA) for caregivers to persons with chronic physical and mental impairments. Res Nurs Health 15(4):271–283. https://doi.org/10.1002/nur.4770150406
26. Vodermaier A, Millman RD (2011) Accuracy of the Hospital Anxiety andDepression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. Support Care Cancer 19(12):1899–1908. https://doi.org/10.1007/s00520-011-1251-4
27. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM (1997) A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 27(2):363–370
28. Joseph O, Alfons V, Rob S (2007) Further validation of the Maudsley Marital Questionnaire (MMQ). Psychol Health Med 12(3):346–352. https://doi.org/10.1080/13548500600855481
29. Nijboer C, Triemstra M, Tempelaar R, Sanderman R, van den Bos GA (1999) Measuring both negative and positive reactions to giving care to cancer patients: psychometric qualities of the Caregiver Reaction Assessment (CRA). Soc Sci Med 48(9):1259–1269. https://doi.org/10.1016/s0277-9536(98)00426-2
30. Traa MJ, Braeken J, De Vries J, Roukema JA, Orsini RG, Den Oudsten BL (2015) Evaluating quality of life and response shift from a couple-based perspective: a study among patients with colorectal cancer and their partners. Qual Life Res 24(6):1431–1441. https://doi.org/10.1007/s11136-014-0872-8

31. Law E, Levesque JV, Lambert S, Girgis A (2018) The "sphere of care": a qualitative study of colorectal cancer patient and caregiver experiences of support within the cancer treatment setting. PLoS One 13(12):e0209436. https://doi.org/10.1371/journal.pone. 0209436
32. Cotrim H, Pereira G (2008) Impact of colorectal cancer on patient and family: implications for care. Eur J Oncol Nurs 12(3):217–226. https://doi.org/10.1016/j.ejon.2007.11.005
33. Ohlsson-Nevo E, Andershed B, Nilsson U, Anderzen-Carlsson A (2012) Life is back to normal and yet not – partners' and patient's experiences of life of the first year after colorectal cancer surgery. J Clin Nurs 21(3–4):555–563. https://doi.org/10.1111/j.1365-2702. 2011.03830.x
34. Maguire R, Hanly P, Hyland P, Sharp L (2018) Understanding burden in caregivers of colorectal cancer survivors: what role do patient and caregiver factors play? Eur J Cancer Care (Engl) 27 (1). doi:https://doi.org/10.1111/ecc.12527
35. Nijboer C, Triemstra M, Tempelaar R, Sanderman R, van den Bos GA (1999) Determinants of caregiving experiences and mental health of partners of cancer patients. Cancer 86(4):577–588
36. Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J, Souglakos J, Shi Q, Kerr R, Labianca R, Meyerhardt JA, Vernerey D, Yamanaka T, Boukovinas I, Meyers JP, Renfro LA, Niedzwiecki D, Watanabe T, Torri V, Saunders M, Sargent DJ, Andre T, Iveson T (2018) Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med 378(13):1177–1188. https://doi.org/10.1056/NEJMoa1713709
37. van de Wal M, Langenberg S, Gielissen M, Thewes B, van Oort I, Prins J (2017) Fear of cancer recurrence: a significant concernamong partners of prostate cancer survivors. Psycho-oncology 26(12):2079–2085. https://doi.org/10.1002/pon.4423
38. Jansen L, Dauphin S, De Burghgraeve T, Schoenmakers B, Buntinx F, van den Akker M (2019) Caregiver burden: an increasing problem related to an aging cancer population. J Health Psychol:1359105319893019. https://doi.org/10.1177/1359105319893019
39. Palacio C, Krikorian A, Limonero JT (2018) The influence of psychological factors on the burden of caregivers of patients with advanced cancer: resiliency and caregiver burden. Palliat Support Care 16(3):269–277. https://doi.org/10.1017/S1478951517000268

Chapter 4

Caregivers of patients receiving long-term treatment with a tyrosine kinase inhibitor (TKI) for gastrointestinal stromal tumour (GIST): a cross-sectional assessment of their distress and burden

Simone M.C.H. Langenberg, An K.L Reyners, Anke N.M. Wymenga, Gerry C.M. Sieling, Carel M.M Veldhoven, Carla M.L. van Herpen, Judith B. Prins, Winette T.A. van der Graaf

Acta oncologica (2019) 58 (2): 191-199

ABSTRACT

Introduction: TKIs are a long-term treatment for GIST, and may have an impact on caregivers.

Material and Methods: For this cross-sectional study, patients and caregivers were both included when patients had been treated with TKIs for at least six months. Caregivers completed questionnaires including demographics, distress (Hospital Anxiety and Depression scale), burden (Self-Perceived Pressure from Informal Care) general health (RAND-36), comorbidity (Self-administered Comorbidity Questionnaire), social support (Social Support List – Discrepancies) and marital satisfaction (Maudsley Marital Questionnaire). Patients completed similar questionnaires, without 'burden'. We conducted analyses to explore differences between caregivers with low/moderate versus high levels of burden and low versus high levels of distress.

Results: Sixty-one out of seventy-one eligible couples (84%) were included in the analysis. The median age of the caregivers was 60 years; 66% were female and 78% were the patients' spouse. The median age of the patients was 66 years; 43% were female. Caregivers experienced high levels of burden and distress in 10% and 23%, respectively. Caregivers with high levels of burden perceived significantly lower mental health, less vitality, lower general health and high levels of distress. Significantly higher levels of burden were found in non-spouses, caregivers of patients with more treatment-related side effects, caregivers who spent more hours caring, and those caring for more than one person. For distress, caregivers with high levels of distress perceived significantly more burden, lower social functioning, more role physical and emotional problems, lower mental health, less vitality and lower general health. Furthermore, high levels of distress were found in caregivers of more dependent patients and those caring for more than one person.

Conclusions: Caregivers of the patients with GIST treated with TKI are managing well. There is a small, vulnerable group of caregivers with high levels of burden and/or distress, who show more health-related problems, both physical and mental, and require adequate support.

INTRODUCTION

Gastro-intestinal stromal tumours (GIST) belong to the rare and heterogeneous group of soft tissue sarcomas. Curative treatment consists of radical surgery, in high risk tumours combined with (neo) adjuvant imatinib [1]. Currently, the duration of adjuvant therapy is three years [2]. Until 2000, the treatment of GIST was limited, as GIST are resistant to chemo- and radiotherapy. In 2000, imatinib, a tyrosine kinase inhibitor (TKI), was introduced as the first targeted treatment for metastatic GIST. This significantly improved median overall survival from <1 year to >5 years nowadays, causing a change in life perspective for these patients [2]. Imatinib in GIST has been a successful, often prolonged, targeted treatment for GIST, both in the adjuvant and metastatic setting. More attention has recently been given to the chronicity of the disease, including the need for treatment with other TKIs when resistance to imatinib develops. This had led to the so called Sword of Damocles, fear of recurrence or progression [3]. The approach to GIST patients and their caregivers and their needs had therefore evolved [4]. Chronic oral treatment may be accompanied by side effects, such as, fatigue, diarrhoea, nausea, periorbital oedema, muscle cramps and skin rash [5]. These adverse events, frequent radiological evaluations and related uncertainties may have an impact on patients' personal lives. We previously demonstrated that around one third of GIST patients on TKIs experience high levels of fear of cancer recurrence or progression. They also experience high levels of distress, functional impairment (emotional, social, cognitive) and have difficulties making plans for the future [3].

In a study of prostate cancer patients, treated with curative intent, we found that fear of cancer recurrence did not only adversely affect patients, but also their caregivers [6]. Little is known about how GIST and its (chronic) treatment may impact informal caregivers, while chronic fatigue, nausea and diarrhoea may conceivably impact the partner or the family. Studies have shown that cancer not only affects the individual patient and caregiver separately, but also their intertwined life as a couple [7,8]. Patients' longer-term mechanisms for coping with cancer and its treatment are influenced by difficulties experienced by their caregivers. Caregivers may even perceive levels of burden, distress, anxiety and decreased social support that are greater than the patient during the cancer treatment trajectory [8].

Burden is defined by Zarit et al., and mentioned in the review of Adelman et al., as 'the extent to which caregivers perceive that caregiving has had an adverse effect on their emotional, social, financial, physical and spiritual functioning' [9,10]. This definition shows that burden is a multidimensional experience. Known risk factors for higher levels of perceived burden are diverse, but most well recognized are demographic factors, such as being female and living with the recipient of care,

psychosocial factors (especially depression), fewer coping strategies and social isolation [10]. Furthermore, patient distress, spending more hours caring for the patient, financial stress, a lack of choice in becoming a caregiver and discontinuation of their own employment are risk factors [10]. High levels of burden may negatively interfere with the caregivers' general health, both physical and mental [11,12]. Distress, defined by the National Cancer Institute as 'emotional, social, spiritual of physical pain or suffering that may cause a person to feel sad, afraid, depressed, anxious or lonely', is an important psychological morbidity, which often coincides with burden [10,13]. Risk factors for distress are wide ranging, however worry about treatment efficacy, managing side effects, social isolation, lack of preparation in caring for a significant other and complexity of care are identified as more specific for caregivers of patients on active treatment for cancer [13].

With this cross-sectional study, we aim to explore the well-being of caregivers of patients with chronic TKI treatment, by measuring burden, distress, general health, discrepancies in social support and marital satisfaction. Furthermore, we will explore whether there are the differences in caregivers experiencing high levels of burden and distress versus caregivers with low/moderate levels of burden and low levels of distress. To the best of our knowledge, this is the first study exploring well-being of caregivers of patients with GIST treated with TKIs, and is also one of the few studies exploring caregivers' well-being during long-term oral anticancer treatment.

MATERIAL AND METHODS

Setting and participants

The cross-sectional study was conducted between June 2013 and May 2014 in the Departments of Medical Oncology at three hospitals in different regions of the Netherlands; two university medical centres and one regional hospital. Inclusion criteria for patients were: age older than 18 years, able to communicate in Dutch language, TKI treatment for at least six months in either the adjuvant or palliative setting, having an informal caregiver. Exclusion criteria for the patients were: prognosis of less than 12 weeks, able to communicate in Dutch language, no informal caregiver. A caregiver was defined as a person who cared for a patient during their chronic treatment with a TKI for GIST. This included a spouse, sibling, friend or other relative. Inclusion criteria for caregivers were: age older than 18 years. Exclusion criteria for caregivers were: not able to communicate in Dutch language. When either the patient or the caregiver met the one of the exclusion criteria, both were excluded.

Procedure

The study was approved by the local medical ethical committee (Radboud University Medical Centre 2013/278). All patients in the database of the Departments of Medical Oncology of the attending hospitals were systematically assessed for their eligibility by their attending physician. The attending physician approached the patient and their caregiver during an outpatient follow-up visit or by telephone. When the patient and the informal caregiver gave their verbal informed consent, they were included. They were both asked to a single complete self-report questionnaires, independently of each other. Completing the paper and pencil questionnaire took between 45 and 60 min. Data were analysed anonymously.

Questionnaires

Demographics

Demographic characteristics were obtained with a questionnaire, including gender, age, nationality, education, employment and relationship with each other (spouse, sibling, offspring, friend). We inquired whether the patient experienced side effects of TKI treatment (answer possibilities: 'no, I do not experience side effects', 'yes, I do experience side effect, but they are not bothersome', 'yes, I do experience side effects and they are bothersome', 'yes, I do experience side effects and they are extremely bothersome') and whether the patient experienced difficulties enduring long-term TKI treatment (answer possibilities: 'no', 'yes, a little bit', 'yes', 'yes, it is very difficult'). The caregiver answered questions regarding caregiving-related topics, including patients' independence, hours of caring, caring for more people than the patient, change in own health as a consequence of giving care, and neglecting own health as a consequence of being a caregiver. Duration and setting ((neo-) adjuvant or palliative) of treatment was reported by the attending physician.

Questionnaires assessing general health

The RAND-36 Health Survey is a validated, 36-item questionnaire assessing functional status, well-being and general health on eight subscales: (1) physical functioning (i.e., activities of daily living; 10 items), (2) social functioning (i.e., limitations in normal social functioning due to physical and emotional functioning), (3) role-physical (i.e., limitations in work and activity of daily living due to physical problems), (4) role-emotional (i.e., limitations in work and activity of daily living due to emotional problems), (5) mental health (i.e., regarding feelings of sadness and anxiety), (6) pain (i.e., experience of pain and limitations of activities of daily living as a consequence of pain), (7) vitality (i.e., feelings of energy and tiredness) and (8) general health (i.e., subjective evaluation of personal general health). Scores on

each subscale are transformed into a range from 0 to 100. Higher scores indicate higher levels of functioning, well-being and general health. The Dutch version of the questionnaire has been validated and showed sufficient to good internal consistency (Cronbach's a 0.71–0.92) [14].

The Self-administered Comorbidity Questionnaire is a questionnaire, assessing whether comorbidity is present, and if so, is treated and/or leads to impairments in daily functioning. The questionnaire consists of 14-items with defined medical conditions and three blank spaces to complete when a medical condition is present, but not defined in the 14-items [15].

Questionnaires assessing mental health and social support

The Hospital Anxiety and Depression Scale (HADS) is a validated, 14-item self-assessment questionnaire to assess psychological distress [16,17]. Total scores range between 0 and 42. Each item is rated on a scale from 0 (not at all) to 3 (very much). Higher scores indicate higher levels of distress. To identify high levels of distress on an individual basis, for patients we used the validated cutoff score for cancer patients of 11 or higher [18]. For caregivers, a cutoff score of 12 was used. This cutoff score is validated in several Dutch populations and used in other clinical studies in with cancer caregivers in the Netherlands [16,19].

The Social Support List – Discrepancies (SSL-D) contains 34-items to assess discrepancies between an individual's' need for social support and their perceived social support. The questionnaire assesses six types of social support, namely emotional interactions, problem-focused emotional support, esteem support, instrumental interactions, social companionship and informational support. The main question is 'Does it ever occur that people…', which is followed by a statement, for example 'offer you mental support' or 'offer you good advice' or 'offer you constructive feedback'. The answer possibilities are (1) 'I miss this, I would like to receive this more often', (2) I do not miss this, but it would be fortunate to receive this more often, (3) The support meets my needs exactly, (4) This happens too often, it would be fortunate when it happens less. The score on every item is transformed to scores ranging from 34 to 136, with higher scores indicating more unmet need for social support [20,21].

Marital satisfaction was measured with the 'marital satisfaction' subscale of the Maudsley Marital Questionnaire (MMQ), a validated questionnaire to assess marital satisfaction. This is a 10-item questionnaire, answered on a 9-point scale (0–8), ranging from 0 to 80. Higher scores indicate decreased marital satisfaction [22]. We instructed participants of this study only to complete this questionnaire if they were a couple.

Questionnaire assessing giving care to a significant other

The Self-Perceived Pressure from Informal Care (SPPIC) is a Dutch, validated questionnaire to assess caregivers' self-perceived stress as a reaction to providing informal care. In the Netherlands, the questionnaire is often used among cancer caregivers to measure their perceived burden during patients' treatment. The questionnaire assesses how perceived pressure as a consequence of giving care to a significant other interferes with caregivers' personal interests, where 'personal interest' is defined as the possibility to have own thoughts, activities and/or other roles they want to fulfil in life. Examples of questions are 'As a consequence of the situation of my significant other, less time is available managing my personal life' or 'Combining the responsibility for my significant other and my family and work is challenging'. It consists of a nine-item, five-point Rasch scale. According to the questionnaire manual, the scores are dichotomized to 0 ('no!' and 'no') and 1 ('yes!', 'yes' and 'more or less'). The total scores range from 0 to 9, with higher scores indicating high levels of burden [23]. Total scores on the scale were defined as low (0–3), moderate (4–6) and high levels of burden. (7–9) This was in accordance with a study performed among caregivers of patients with oesophageal cancer [24].

Statistical analyses

Analyses were performed using SPSS software version 20 (SPSS Inc. Chicago, IL, USA). For analysis, incomplete dyads were excluded. Descriptive statistics were used for sample characteristics. To explore the association between patients' distress and caregivers' burden and distress, Pearsons correlations were performed. For the analysis of low/moderate versus high levels of burden and low versus high levels of distress, we performed independent-samples T-test for continuous variables when equal distribution of the number of participants between group was expected. The Mann–Whitney U test was performed when normal distribution was not met between groups. For categorical variables, Chi-square tests were performed and Fisher's exact test was conducted when the condition of a maximum of 20% with ≤ 5 expected counts was not met. We explored whether there was a difference between low/moderate (score 0–6) versus high levels (7–9) of burden for the following variables: age, gender, relation to patient (spouse versus non-spouse), employment (yes/no), independence patient (yes/no), caring for more people than the patient with GIST (yes/no), hours of caring (<8h/>8 h), duration of TKI use (months), setting of TKI use (adjuvant versus palliative), side effects of TKI use (yes/no), caregivers' comorbidity (yes/no), distress (HADS), discrepancies in social support (SSL-D), general health (RAND-36) and marital satisfaction (MMQ). We applied all the same variables to explore differences between high and low levels of distress, where distress (HADS) was replaced for burden (SPPIC). For all analysis, a p-value of <0.05 was considered as a statistically significant difference.

RESULTS

Caregivers' and patients' characteristics

Seventy-one couples were eligible, of whom 61 (84%) couples participated by returning the completed questionnaires. Reasons for not participating in the study were the expectation that filling out the questionnaires was too confronting (two couples) and unknown reason (eight couples). Table 1 shows caregivers' and patients' demographic characteristics, patients' treatment-related characteristics and caregiving-related characteristics. The median age of caregivers' was 60 years; 66% were female and 78% were the patient's' spouse. The median age of patients was 66 years, and 43% were female. The mean duration of patients' treatment with a TKI was 44 months (SD=34).

Table 1. Caregivers' and patients' characteristics (n=61)

Characteristics participants	Details	Caregiver, n (%)	Patient, n (%)
Gender	Female	40 (66)	26 (43)
Age, median	Years (IQR)	60 (51-68)	66 (55-75)
Educational level [a]	Lower education (ISCED < 4)	36 (60)	41 (67)
	Higher education (ISCED > 4)	24 (40)	20 (33)
Relation to patient [b]	Spouse	46 (78)	
	Sibling	1 (2)	
	Child	11 (19)	
	Friend	1 (2)	
Employment status [c]	Paid work	28 (47)	12 (20)
	Housekeeper	8 (13)	14 (23)
	Voluntary work	5 (8)	7 (12)
	Disablement insurance act	3 (5)	11 (18)
	Retired	22 (37)	27 (44)
TKI treatment duration	Month (SD)		44 (34)
TKI treatment	Adjuvant, n (%)		12 (20)
	Palliative, n (%)		49 (80)
Side effects treatment	No, n (%)		5 (9)
	Yes, minimal, n (%)		24 (41)
	Yes, bothersome, n (%)		25 (42)
	Yes, severe, n (%)		5 (9)

Table 1. Continued

Characteristics participants	Details	Caregiver, n (%)	Patient, n (%)
Difficulties enduring TKI treatment	No, n (%)		40 (66)
	Yes, somewhat, n (%)		12 (20)
	Yes, n (%)		7 (12)
	Yes, serious, n (%)		1 (2)
Hours of caregiving (weekly), n (%)	< 8, n (%)	47 (84)	
	8-16, n (%)	5 (9)	
	16-24, n (%)	0 (0)	
	>24, n (%)	4 (7)	
Patients' independence, n (%)	Completely independent	42 (69)	
	Mostly independent	14 (23)	
	Partly independent, partly dependent	4 (6)	
	Mostly dependent	1 (2)	
Caregiving to other people, other than patient [a]	Yes	9 (15)	
	No	51 (85)	
General health changed as a consequence of giving care	Yes	1 (2)	
	Somewhat	9 15)	
	No	51 (84)	
Neglecting own health as a consequence of giving care	Yes	1 (2)	
	Somewhat	8 (13)	
	No	52 (85)	
Number of comorbidities	0	18 (30)	13 (21.3)
	1	19 (31)	15 (24.6)
	2	13 (21)	18 (29.5)
	3	5 (8)	6 (9.8)
	4	3 (5)	2 (3.3)
	5	1 (2)	4 (6.6)
	6	1 (2)	3 (4.9)
	7	1 (2)	0 (0)

IQR = interquartile range; ISCED = International Standard Classification of Education; SD = standard deviation; [a] One missing; [b] two missing; [c] more than one option possible

Caregivers' general health (RAND-36), comorbidities (SCQ), burden (SPPIC), distress (HADS), marital satisfaction (MMQ) and discrepancies between need for social support and perceived social support (SSL-D)

Overall, scores on the RAND-36 showed that caregivers' general health was not significantly different from values of normative comparatives, except for pain, which was significantly worse (p<.001). Details are shown in Table 2. The number of comorbidities affecting caregivers ranged from 0 (29.5%) to 7 (1.6%), with most between 0 and 2 (84%); 70% had one or more comorbidit(y)(ies). An overview of the number of comorbidities is given in Table 1. An overview of the nature and treatment of comorbidities, is shown in Table 3.

The mean score for burden was 2.4 (SD=2.3; range 0–9). Seventy-four percent (n=45) reported low, 16% (n=10) moderate and 10% (n=6) high levels of burden. Of the caregivers who reported low levels of burden, 18% (n=11) experienced no burden at all. The mean level of distress was 8.1 (SD=5.7; range 0–42) and 23% of the caregivers experienced high levels of distress. Discrepancies in social support showed a mean score of 39.2 (SD=6.7; range 34–136). Mean score for marital satisfaction was 9.3 (SD 9.3; range 0–80).

Caregivers' burden was significantly correlated with their own distress (r=0.584, p<0.01) and patients' distress (r=0.442, p<0.01). Furthermore, caregivers' distress was significantly correlated with patients' distress (r=0.375, p<0.01).

Table 2. RAND-36 Health Survey outcomes of caregivers and patients in relation to healthy population [14]

RAND subscale	Caregiver mean scores (SD)	Patient mean scores (SD)	Healthy population mean scores (SD)
Physical functioning	87.6 (19.9)	69 (21.2) *	81.9 (23.2)
Social functioning	83.5 (16.7)	77.5 (24.8) *	86.9 (20.5)
Role physical	83.2 (30.1)	63 (43.4) *	79.4 (35.5)
Role emotional	87.9 (28.4)	69.4 (42.6) *	84.1 (32.3)
Mental health	77.2 (15.8)	76.3 (15.7)	76.8 (18.4)
Pain	49.1 (5.4) *	48.1 (7.6) *	79.5 (25.6)
Vitality	70.1 (17.5)	61 (19.1) *	67.4 (19.9)
General health	72.7 (17.8)	49.4 (20.9) *	72.7 (22.7)

RAND = Rand-36 Health Survey; SD = standard deviation; * Significantly different from healthy population at p<0.01 level

Table 3. Caregivers' comorbidities, treatment and perceived limitations in daily life

Comorbidity	Total, n (%)	Treatment, n (% of total)	Impairments in daily functioning, n (% of total)
Heart disease	7 (12)	7 (100)	4 (57)
Stroke	0 (0)	0 (0)	0 (0)
Hypertension	12 (20)	10 (83)	0 (0)
Asthma, chronic bronchitis, COPD	4 (7)	2 (33)	1 (25)
Diabetes	1 (2)	1 (100)	0 (0)
Stomach ulcer	0 (0)	0 (0)	0 (0)
Kidney disease	0 (0)	0 (0)	0 (0)
Liver disease	0 (0)	0 (0)	0 (0)
Anaemia or other blood diseases	0 (0)	0 (0)	0 (0)
Cancer	2 (3)	1 (50)	0 (0)
Thyroid disease	2 (3)	2 (100)	1 (50)
Depression	4 (7)	1 (25)	3 (75)
Arthrosis	17 (28)	6 (40)	8 (57)
Back pain	15 (25)	5 (36)	8 (57)
Rheumatoid arthritis	3 (5)	1 (33)	1 (50)
Other	23 (37)	13	10

COPD = chronic obstructive pulmonary disease

Patients' general health (RAND-36), comorbidities (SCQ), distress (HADS), marital satisfaction (MMQ) and discrepancies between need for social support and perceived social support (SSL-D)

Patients' general health was significantly different to normative comparatives for every dimension measured, except for mental health, which was comparable. Details are shown in Table 2. The number of comorbidities affecting patients ranged from 0 (21.3%) to 6 (4.9%), with the most between 0 and 3 (85.2%); 78.7% had one or more comorbidit(y)(ies). Details are given in Table 1. Overall, the mean level of patients' general distress was 9.6 (SD=6.8; range 0–42) and 34% of patients experienced high levels of distress. Discrepancies in social support showed a mean score of 38.7 (SD=6.2; range 34–136). For marital satisfaction patients reported a mean score of 9.3 (SD=10.0; range 0–80).

Exploring caregivers' high levels of burden and distress

When the caregivers who experienced high burden (n=6, 10%) were compared to caregivers with low and moderate burden (n=55, 90%), the caregivers with high levels of burden experienced significantly more distress (p=0.003), lower mental health (p=0.033), less vitality (p=0.019) and lower general health (p=0.038). High levels of burden were found in non-spouses (p=0.017), caregivers of patients experiencing more treatment side effects (p=0.016), those who spent more hours caring (p=0.046) and those who were caring for more than one person (p=0.038). All caregivers with high levels of burden, had one of more comorbidit(y)(ies). Details are shown in Table 4.

Table 4. Overview of demographical, treatment-related, care-related and health-related variables of caregivers stratified for low/moderate levels versus high levels of burden

Variables		Low / moderate levels of burden, n=55	High levels of burden, n=6	P value
Gender	Male, n (%)	20 (95.2)	1 (4.8)	0.654
	Female, n (%)	35 (87.5)	5 (12.5)	
Relation to patient	Spouse, n (%)	45 (95.7)	2 (4.3)	0.017*
	Non spouse, n (%)	9 (69.2)	4 (30.8)	
Employment	Yes, n (%)	25 (89.3)	3 (10.7)	1.000
	No, n (%)	29 (90.6)	3 (9.4)	
Side effects	Yes, n (%)	22 (81.5)	5 (18.5)	0.016*
	No, n (%)	32 (100)	0 (0)	
Setting TKI use	Adjuvant, n (%)	12 (100)	0 (0)	0.588
	Palliative, n (%)	43 (87.8)	6 (12.2)	
Independence patient	Yes, n (%)	52 (92.9)	4 (7.1)	0.071
	No, n (%)	3 (60)	2 (40)	
Hours of caring	< 8 hours, n (%)	44 (93.6)	3 (6.4)	0.046*
	> 8 hours, n (%)	6 (66.7)	3 (33.3)	
Caring for more than one person	Yes, n (%)	6 (66.7)	3 (33.3)	0.038*
	No, n (%)	48 (94.1)	3 (5.9)	
Comorbidity caregiver	Yes, n (%)	37 (86)	6 (14)	0.167
	No, n (%)	18 (100)	0 (0)	
Age	Years	31.2	29.5	0.827
Duration TKI treatment	Months	29.2	42.8	0.085
HADS total (caregiver)	Mean ranks	28.9	50.1	0.003**

Table 4. Continued

Variables		Low / moderate levels of burden, n=55	High levels of burden, n=6	P value
SSL-D	Mean ranks	26.9	36.9	0.137
MMQ – marital satisfaction	Mean ranks	23.2	30.5	0.450
RAND physical functioning caregiver	Mean ranks	29.9	30.2	0.977
RAND social functioning caregiver	Mean ranks	31.5	21.3	0.156
RAND role physical caregiver	Mean ranks	29.9	25.2	0.458
RAND role emotional caregiver	Mean ranks	30.2	22.6	0.162
RAND mental health caregiver	Mean ranks	31.1	15.7	0.033*
RAND vitality caregiver	Mean ranks	31.2	14.5	0.019*
RAND pain caregiver	Mean ranks	30.0	24.2	0.483
RAND general health caregiver	Mean ranks	31.1	16.0	0.038*

TKI = tyrosine kinase inhibitor; HADS = Hospital Anxiety and Depression Scale; SSL-D = Social Support List – Discrepancies; RAND = Rand-36 Health Survey; MMQ = Maudsley Marital Questionnaire; *Statistically significant values at p<0.05 level; ** Statistically significant values at p<0.01 level; continuous variables were tested with Mann-Whitney U, mean ranks are reported; categorical variables were tested with Fisher's exact, numbers and percentages are reported.

When caregivers with high levels of distress (n=14, 23%) were compared to caregivers with low levels of distress (n=47, 77%), the caregivers with high levels of distress experienced significantly more burden (p=0.001), lower levels of social functioning (p=0.016), more role physical problems (p=0.007), more role emotional problems (p=0.043), lower levels of mental health (p<0.001), less vitality (p<0 .001), lower levels of general health (p=0.006). Furthermore, high levels of distress were found in caregivers of patients who were perceived as less independent (p=0.008) and in caregivers caring for more than one person (p=0.025). For caregivers with high levels of distress 79% had one or more comorbidit(y)(ies), but there was no difference in whether the caregiver had comorbidities (yes/no) between groups with low versus higher levels of distress. Details are shown in Table 5. The duration of treatment and setting in which the treatment was given (adjuvant or for metastatic GIST) did not differ between caregivers with high or low/moderate levels of burden, nor high and low levels of distress.

Table 5. Overview of demographical, treatment-related, care-related and health-related variables of caregivers stratified for low versus high levels of distress

Variables		Low levels of distress, n=47	High levels of distress, n=14	P value
Gender	Male, n (%)	19 (90.5)	2 (9.5)	0.109
	Female, n (%)	28 (70)	12 (30)	
Relation to patient	Spouse, n (%)	37 (78.7)	10 (21.3)	0.478
	Non spouse, n (%)	9 (69.2)	4 (28.6)	
Employment	Yes, n (%)	23 (82.1)	5 (17.9)	0.547
	No, n (%)	24 (75)	8 (25)	
Side effects	Yes, n (%)	19 (70.4)	8 (29.6)	0.224
	No, n (%)	27 (84.4)	5 (15.6)	
Setting TKI use	Adjuvant, n (%)	9 (75)	3 (25)	1.000
	Palliative, n (%)	38 (77.6)	11 (22.4)	
Independence patient	Yes, n (%)	46 (82.1)	10 (17.9)	0.008**
	No, n (%)	1 (20)	4 (80)	
Hours of caring	< 8 hours, n (%)	37 (78.7)	10 (21.3)	0.206
	> 8 hours, n (%)	5 (55.6)	4 (44.4)	
Caring for more than one person	Yes, n (%)	4 (44.4)	5 (55.6)	0.025*
	No, n (%)	42 (82.4)	9 (17.6)	
Comorbidity caregiver	Yes, n (%)	15 (83.3)	3 (16.7)	0.525
	No, n (%)	32 (74.4)	11 (25.6)	
Age	Years	30.3	33.2	0.595
Duration TKI treatment	Months	31.4	29.7	0.757
SPPIC	Mean ranks	26.8	45.1	0.001**
SSL-D	Mean ranks	27.2	30.7	0.475
MMQ – marital satisfaction	Mean ranks	21.9	29.2	0.131
RAND physical functioning caregiver	Mean ranks	31.5	25.1	0.205
RAND social functioning caregiver	Mean ranks	33.4	21.0	0.016*
RAND role physical caregiver	Mean ranks	32.1	20.6	0.007**
RAND role emotional caregiver	Mean ranks	31.2	24.1	0.043*
RAND mental health caregiver	Mean ranks	35.3	11.3	0.000**
RAND vitality caregiver	Mean ranks	34.1	15.1	0.000**
RAND pain caregiver	Mean ranks	29.9	28.0	0.669
RAND general health caregiver	Mean ranks	31.1	16.0	0.006**

TKI = tyrosine kinase inhibitor; HADS = Hospital Anxiety and Depression Scale; SSL-D = Social Support List – Discrepancies; RAND = Rand-36 Health Survey; MMQ = Maudsley Marital Questionnaire; *Statistically significant values at p<0.05 level; ** Statistically significant values at p<0.01 level; continuous variables were tested with Mann-Whitney U, mean ranks are reported; categorical variables were tested with Fisher's exact, number and percentages are reported.

DISCUSSION

The goal of this study was to explore caregivers' burden and distress during the patients' long-term treatment with TKI for GIST. Overall, caregivers of patients treated for GIST seem to manage well, as their levels of perceived burden and distress are low, their perceived general health is good and similar to the healthy population, their marital satisfaction seems good and they do not seem to experience discrepancies in social support. Fortunately, 90% of caregivers in this study perceived low to moderate levels of burden, of whom 18% did not perceive any burden at all. The burden of caregivers of the patients with cancer differ, but hardly any studies are performed in caregivers of patients treated with long-term TKIs. In a study by Haj Mohammed et al., where caregivers of oesophageal cancer patients were studied for burden approximately 3 years after being treated with curative intent with neo-adjuvant chemoradiotherapy followed by resection, the percentage of low and moderate burden was 81% [24]. In a study by Hsu et al., exploring caregivers' burden of patients treated for cancer in early stage of disease (30%) or advanced disease (70%) for haematological and solid malignancies, low and moderate burden was found in 75% of caregivers [25]. Additionally, the multivariate analyses in the study by Hsu et al. showed that caregivers who were employed and providing support for activities of daily living, were at greater risk of high levels of burden [25]. According to the caregivers in our study, 84% of the caregivers spent less than 8 h weekly providing care to the patient and 92% of GIST patients function independently of their caregivers in daily life, although the questionnaire did not define exactly what is meant by functioning independently. This may explain why the levels of burden in caregivers is perceived as low. Another reason may be that caregivers in our study experience low levels of discrepancies between their need for social support and their perceived social support. It is known that social support is vital in preventing high levels of burden [10]. Furthermore, it is known that good copings skills may protect caregivers from overstretching themselves [10]. As the average duration of treatment of the patients in our sample was 44 months, this may have given caregivers time to adjust to patients' disease and treatment. On the other hand, our study showed that there was no difference between the groups of low/moderate and high levels of burden and low and high levels of distress according to the duration of treatment. This may also suggest that there is a group of caregivers that is not able to adjust over time.

Overall, we found that levels of distress were low. Distress in caregivers of patients on active treatment can arise due to worries about the efficacy of treatment, management of side effects, social isolation, lack of experience when caring for a significant other and complexity of care [13]. Considering these risk factors,

caregivers in our study experienced low levels of unmet needs for social support and the majority of the caregivers spent a low number of hours of providing care, which might protect them from distress. On the other hand, 50% of the patients in this study reported bothersome or severe side effects of treatment and 34% of the patients experienced high levels of distress. The latter was associated with caregivers' levels of distress and burden. This, together with the need for continuous treatment, anxiety about computed tomography (CT) scans and results, may have contributed to high levels of distress in 23% of caregivers.

It is vital that attention is given to caregivers with high levels of distress and burden, as active treatment for patients with GIST is at least three years in the adjuvant setting and may be much longer with metastatic GIST. We identified a group of caregivers with high levels of burden (10%) or distress (23%), and compared them to the group of caregivers with low/moderate levels of burden or low levels of distress. Caregivers with high levels of burden, had significantly lower levels of mental health (i.e., feelings of sadness and anxiety), vitality (i.e., tiredness and lower levels of energy) and general health (i.e., perception of lower quality of personal general health). It is known that high levels of burden are associated with depressive symptoms, or even depression as an outcome, and our findings are therefore consistent with other studies [10,13]. Regarding their general health, 100% of the caregivers with high levels of burden had one or more comorbidities, which is higher than the average for the Dutch population (between 42 and 52% above 55 years) [26]. Nevertheless, there was no significant difference in the number of comorbidities between the group with low/moderate and high levels of burden. This may be explained by the fact that most of the comorbidities reported by caregivers did not cause limitations in daily functioning, except for arthrosis, back pain and rheumatoid arthritis. The latter may explain why caregivers, overall, had significantly higher pain scores on RAND-36 compared with their normative comparatives. Nevertheless, only 2% reported they experienced a decline in their health as a consequence of caring for their significant other.

Caregivers who perceived high levels of burden spent significantly more hours caring for their significant other and were more likely to care for more people other than the GIST patient alone. Adelman et al. described in their review that spending more hours caring is a risk factor for burden and Northouse et al. described that it is associated with disruption to their own lifestyle and interference with their own social activities causing social isolation [10,11]. The latter may on its own contribute to distress, as we found that caregivers with high levels of distress had significantly more problems with social functioning. It may be that what normally protects caregivers against overstraining, such as moving on with their own life, their employment and social interaction, is insufficient and may lead to (serious) health

problems, as found in other studies [10,13,27]. Furthermore, caregivers experiencing high levels of burden were shown to care for patients who had significantly more treatment-related side effects. An important TKI-related side effect is severe fatigue, which was studied by Poort et al. This study showed that 30% of patients treated with a TKI for GIST were severely fatigued and this influenced their quality of life and impaired their overall functioning [28]. Pitceathly et al. described that caregivers' distress increases when a patient has more physical complaints [27]. It is conceivable that side effects may influence many aspects of a patient's life and therefore also interfere with the well-being of caregivers, as they cope with the disease and its treatment as a couple [7,8].

This study had a number of limitations. Firstly, as far as we know, there are no validated cutoff points for measuring burden and distress in caregivers with the SPPIC and HADS, respectively. The SPPIC is a validated instrument to measure burden and is often used in clinical settings to measure cancer caregivers' burden. However, no reference data are available and there are no studies performed establishing validated cutoff scores. Nevertheless, for clinical practice, mean scores are often more difficult to interpret and during consultation it is useful to evaluate whether a caregiver experiences moderate or high levels of burden, in order to prioritise the need for support. Therefore, we decided to dichotomise with low and moderate versus high levels of burden, as with the study performed by Haj Mohammed et al. [24] Using this, we tried to identify the most vulnerable group of caregivers and explore risk factors for high levels of burden. Future studies could also focus on the group with moderate levels of burden or decide to combine moderate and high levels of burden, since moderate levels of burden could be of importance for caregivers of patients on long-term treatment. The HADS is also a validated questionnaire and often used to screen for distress among caregivers in clinical practice in the Netherlands. As for burden, to evaluate whether a caregiver experiences distress, a cutoff score could be helpful, however, there are no established cutoff scores to measure higher levels of caregivers' distress. Therefore, we adopted a cutoff score of 12, which is often used when screening for distress in general practice, and seems to have a satisfactory sensitivity for the total HADS scale, important for preventing too many false negatives [16]. We acknowledge that the HADS is especially useful as a first screening for distress and we want to emphasize that it is important to explore the cause of distress further when finding cases using cutoff scores.

In order to explore differences between low/moderate and high levels of burden and low and high levels of distress, we used multiple separate tests. With these tests we can only explore whether there were differences between the groups, without drawing conclusions about its cause or associations between

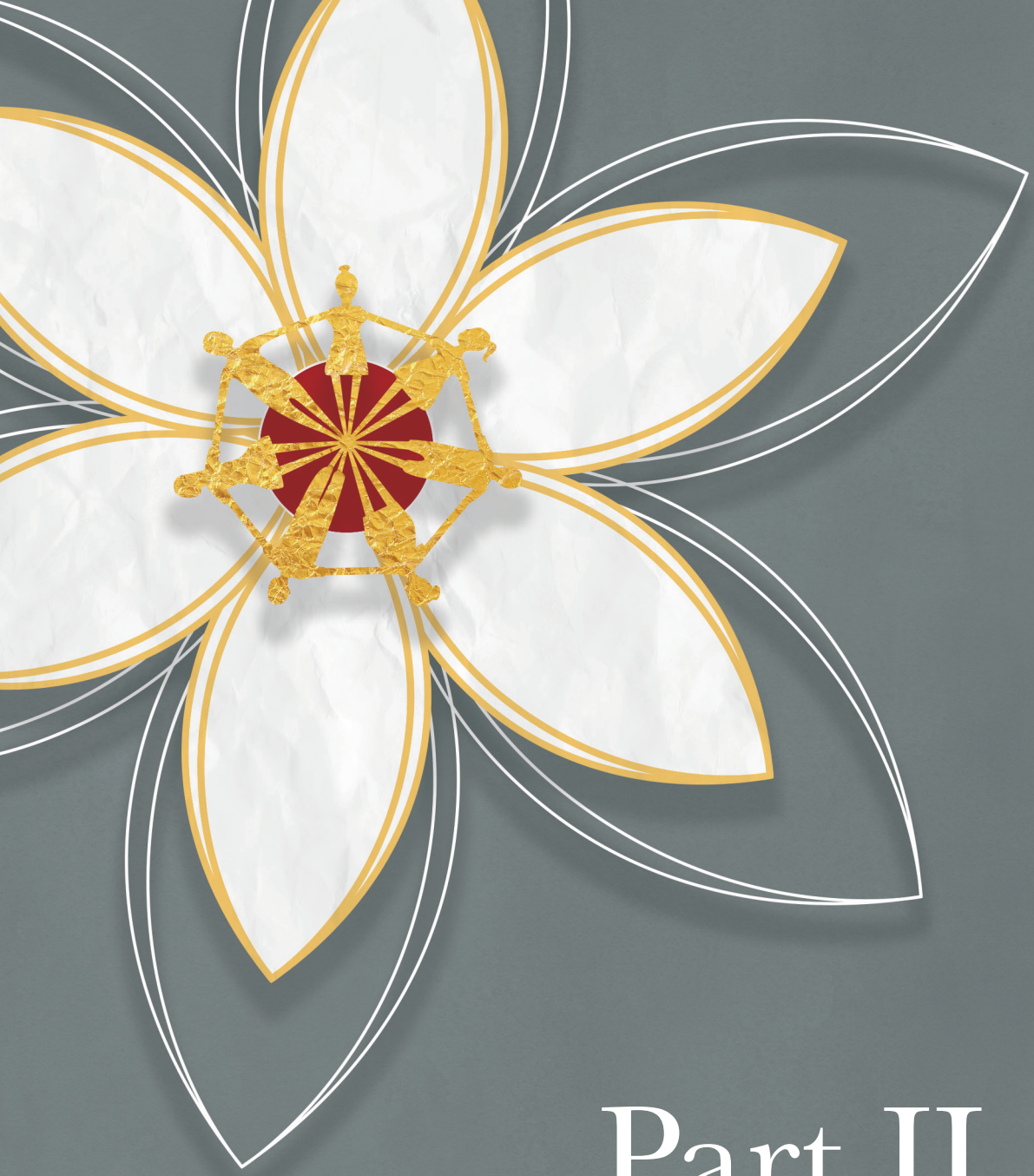
variables. To determine association between the variables and possible causes of burden and distress, a multiple regression analysis would be of added value. Due to our small sample size we did not perform multiple regression analyses. The generalizability of this study may also be limited due to the small sample size. Future studies could perform these analyses with a larger sample size in order to prevent type II error. These studies could focus on this association to better understand burden and distress in this group of caregivers, using multiple regression analyses. This was a cross-sectional study and therefore, we cannot draw firm conclusions about causality. We also included both patients receiving curative, i.e., adjuvant, and palliative treatment, however this did not translate in differences in perceived burden and distress. We only studied a group of patients who were on TKI treatment for at least six months and had a prognosis of >12 weeks. Therefore, our results cannot be generalised to caregivers of patients at the start of TKI treatment or caregivers of GIST patients in the terminal phase of their lives. Our sample also did not include caregivers who were under the age of 18 years and were not able to communicate in the Dutch language. These caregivers could be another interesting group of caregivers and it would be interesting to study them in the future. Lastly, there were two couples who did not want to participate as they felt that the questionnaires were too confronting. It is conceivable that these patients and/or caregiver may suffer from burden and/or distress. It is therefore possible that the levels of distress and burden might be even higher than observed in this study.

In conclusion, caregivers of patients on long-term treatment for GIST with TKIs appear to manage well. Nevertheless, it is important to recognise caregivers who have high levels of burden and distress, associated with physical and mental health-related problems. Interestingly, the stage of disease for which the patient was treated, and the duration of the treatment, did not seem to impact the burden and distress, however treatment-related side effects and more hours of caring were related. Healthcare professionals currently aim to involve caregivers in patient care through providing adequate information on how to deal with patients' treatment. Awareness of caregivers' health problems should be improved. Recognizing the burden and distress is an important initial step, however management may be challenging. Future research could focus on how to implement screening for caregivers' burden and distress, how to identify caregivers at high risk for burden and distress, and how to work with other professionals, including general practitioners, in caring for the caregiver.

REFERENCES

1. Joensuu H. Adjuvant therapy for high-risk gastrointestinal stromal tumour: considerations for optimal management. Drugs. 2012;72: 1953–1963.
2. Joensuu H, Wardelmann E, Sihto H, et al. Effect of KIT and PDGFRA Mutations on Survival in Patients With Gastrointestinal Stromal Tumors Treated With Adjuvant Imatinib: An Exploratory Analysis of a Randomized Clinical Trial. JAMA Oncol. 2017;3: 602–609.
3. Custers JA, Tielen R, Prins JB, et al. Fear of progression in patients with gastrointestinal stromal tumors (GIST): Is extended lifetime related to the Sword of Damocles? Acta Oncologica. 2015;54: 1202–1208.
4. Casali PG, Zalcberg J, Le Cesne A, et al. Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels. JCO. 2017;35:1713–1720.
5. Sodergren SC, White A, Efficace F, et al. Systematic review of the side effects associated with tyrosine kinase inhibitors used in the treatment of gastrointestinal stromal tumours on behalf of the EORTC Quality of Life Group. Crit Rev Oncol Hematol. 2014; 91:35–46.
6. van de Wal M, Langenberg S, Gielissen M, et al. Fear of cancer recurrence: a significant concern among partners of prostate cancer survivors. Psychooncology. 2017;26:2079–2085.
7. Kim Y, van Ryn M, Jensen RE, et al. Effects of gender and depressive symptoms on quality of life among colorectal and lung cancer patients and their family caregivers. Psychooncology. 2015;24: 95–105.
8. Northouse LL, Mood D, Templin T, et al. Couples' patterns of adjustment to colon cancer [Research Support, U.S. Gov't, P.H.S.]. Soc Sci Med. 2000;50:271–284.
9. Zarit SH, Todd PA, Zarit JM. Subjective burden of husbands and wives as caregivers: a longitudinal study. Gerontologist. 1986;26: 260–266.
10. Adelman RD, Tmanova LL, Delgado D, et al. Caregiver burden: a clinical review. JAMA. 2014;311:1052–1060.
11. Northouse L, Williams AL, Given B, et al. Psychosocial care for family caregivers of patients with cancer [Review]. J Clin Oncol. 2012;30:1227–1234.
12. Bevans M, Sternberg EM. Caregiving burden, stress, and health effects among family caregivers of adult cancer patients. JAMA. 2012;307:398–403.
13. Northouse LL, Katapodi MC, Schafenacker AM, et al. The impact of caregiving on the psychological well-being of family caregivers and cancer patients. Semin Oncol Nurs. 2012;28:236–245.
14. Zee KI, Sanderman R, Heyink JW, et al. Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med. 1996;3:104–122.
15. Sangha O, Stucki G, Liang MH, et al. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. 2003;49: 156156–156163.
16. Spinhoven P, Ormel J, Sloekers PP, et al. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27:363–370.

17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–370.
18. Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis [Meta-Analysis Research Support, Non-U.S. Gov't Review]. Support Care Cancer. 2011;19:1899–1908.
19. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, et al. Distress in spouses and patients after treatment for head and neck cancer. The Laryngoscope. 2007;117:238–241.
20. Bridges KR, Sanderman R, van Sonderen E. An English language version of the social support list: preliminary reliability. Psychol Rep. 2002;90:1055.
21. VanSonderen E. Het meten van sociale steun met de Sociale Steun Lijst - Interacties (SSL-I) en Sociale Steun Lijst -Discrepanties (SSL-D): een handleiding. Dutch: Tweede herziene druk; 2012.
22. Arrindell WA, Emmelkamp PM, Monsma A, et al. The role of perceived parental rearing practices in the aetiology of phobic disorders: a controlled study. The British Journal of Psychiatry. 1983; 143:183–187.
23. Pot AM, van Dyck R, Deeg DJ. [Perceived stress caused by informal caregiving. Construction of a scale] [Research Support, Non-U.S. Gov't]. Tijdschrift Voor Gerontologie en Geriatrie 1995;26: 214–219.
24. Haj Mohammad N, Walter AW, van Oijen MG, et al. Burden of spousal caregivers of stage II and III esophageal cancer survivors 3 years after treatment with curative intent. Supportive care in cancer: official journal of the Multinational Association of. Support Care Cancer. 2015;23:3589–3598.
25. Centraal bureau voor de Statistiek [cited 2017 Dec 12]. Available from: http://statline.cbs.nl/statweb/publication/?vw=t&dm=slnl&pa=83005ned&d1=0-52&d2=013&d3=0&d4=l&hd=160314-1445&hdr=g2,g3,g1&stb=t
26. Hsu T, Loscalzo M, Ramani R, et al. Factors associated with high burden in caregivers of older adults with cancer [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. Cancer 2014;120:2927–2935.
27. Pitceathly C, Maguire P. The psychological impact of cancer on patients' partners and other key relatives: a Review. European Journal of Cancer. 2003;39:1517–1524.
28. Poort H, van der Graaf WT, Tielen R, et al. Prevalence, impact, and correlates of severe fatigue in patients with gastrointestinal stromal tumors. J Pain Symptom Manage. 2016;52:265–271.



Part II

Informal caregivers of patients after treatment

Chapter 5

Fear of cancer recurrence: a significant concern among partners of prostate cancer survivors

Marieke van de Wal, Simone M.C.H. Langenberg, Marieke F.M. Gielissen, Belinda Thewes, Inge M. van Oort, Judith B. Prins

Psycho-Oncology (2017) 26 (12): 2079-2085

ABSTRACT

Introduction: The aims of the study were to (1) describe the prevalence of fear of cancer recurrence (FCR) in partners of prostate cancer (PCa) survivors; (2) to compare the proportions of high FCR in partners with high FCR in PCa survivors; (3) to explore partners' demographic and survivors' clinical characteristics associated with high FCR in partners; and (4) to identify the relationship between high FCR and health-related quality of life (HRQoL) in partners.

Methods: Questionnaires were sent to partners of disease-free PCa survivors. Outcomes included FCR severity (Cancer Worry Scale [CWS]) and HRQoL (RAND-36). The t and chi-square tests were used to compare partner FCR with survivor FCR. Regression analyses were performed to determine if demographic and clinical characteristics were significantly associated with partner FCR. The multivariate analysis of variance identified differences in HRQoL between partners with high and low FCR.

Results: Questionnaires were completed by 168 partners. Mean levels of FCR were comparable between partners and survivors ($p=0.144$). Thirty-five percent of partners reported high FCR (CWS≥14) compared to 38% of PCa survivors (CWS≥13) ($p=0.542$). Higher survivor FCR and younger partner age were significantly associated with higher partner FCR. Partners with high FCR scored significantly lower on social functioning, emotional role functioning, mental health, general health, and vitality than those with low FCR (all $p<0.05$).

Conclusions: Findings from this study illustrate that FCR is a significant concern for partners of PCa survivors. Clinicians should be aware of partner FCR when delivering care to men with PCa.

INTRODUCTION

Cancer survivorship comes with emotional and physical challenges for the cancer survivor and may also affect their carers and family, especially partners [1]. Most partners adjust well to the stress of cancer after treatment has been completed, but a minority faces difficulties [2,3]. For instance, there is some evidence that female partners of cancer survivors perceive more psychological distress and a lower quality of life than male partners [4,5]. Partners may experience a significant physical and emotional care burden such as heightened distress, fatigue, or the worry that the cancer may come back [6,7].

Fear of cancer recurrence (FCR) is the fear, worry, or concern about cancer returning or progressing [8]. The current literature suggests that FCR is a common concern for those who have survived cancer, with moderate to high FCR affecting on average 49% of cancer survivors [9]. For partners of prostate cancer (PCa) survivors, it was found that a third (36%) of them reported high FCR [10]. While FCR has primarily been regarded as a patient concern, partners may also worry about the risk of cancer recurrence or the possibility of losing their loved one to a potential disease recurrence [11]. As no partner-specific FCR models have been proposed, more general FCR models may be suitable for partners as well. For instance, the conceptual FCR model by Lee-Jones et al [12] explains FCR as a multidimensional construct that includes cognitive and emotional processing systems that influence the perception of FCR and lead to behavioural and emotional FCR responses. Also, certain structural characteristics (personality, history) may predispose persons to higher levels of worry or FCR. Partners' psychological reactions to disease and treatment are believed to follow the same underlying processes and Lee-Jones's model may be applicable to them as well [12].

In cancer survivors, high levels of FCR do not improve spontaneously with time [13] and are associated with adverse outcomes of emotional functioning, experienced distress [9], greater utilization of health care [14], and poorer health behaviours (smoking, lower activity levels) [15]. For partners, potential consequences of FCR are less well understood, but given its association with negative outcomes in cancer survivors, it is reasonable to expect a comparable impact on partner well-being.

Currently, there is a paucity of research on what FCR entails in partners of cancer survivors and only 1 study has assessed high levels of fear of progression (FoP) in partners of PCa patients [16]. This study reported that half (51%, n=24) of all partners experienced high FoP at an average of 8.9 months postdiagnosis; especially partners of PCa patients whom had a relapse. This study's sample size was relatively small, and an unreported number of patients had experienced a

recurrence that limits generalizability. The few studies that have addressed FCR in partners of non-PCa survivors often found similar or even greater FCR in partners (or carers) than in survivors themselves [17-21]. Also, help in managing concerns about cancer returning was one of the top 3 cited unmet needs by partners and caregivers of both short and long-term cancer survivors [22,23] with, respectively, 18% and 10% reporting FCR to be an unmet need at 6 and 24 months post survivor diagnosis [23]. Fear of cancer recurrence appeared to be a consistent and core unmet need for many. Furthermore, greater knowledge of factors associated with FCR in partners can be used to guide improvement of care for partners.

The aims of this cross-sectional study were to (1) describe the prevalence of high FCR in partners of PCa survivors; (2) to compare the proportions of partners with high FCR with the proportion of survivors with high FCR; (3) to explore partners' demographic and survivors' clinical characteristics associated with high FCR in partners; and finally, (4) to identify the relationship between high FCR in partners and their health-related quality of life (HRQoL). It was hypothesized that (1) partners experience similar mean levels of FCR as PCa survivors and that (2) an equal proportion of partners and cancer survivors report high FCR. On the basis of the available literature,8,24 we expect that (3) a younger age to be significantly associated with FCR in partners and that (4) partners with high FCR report a poorer HRQoL.

METHODS

Sample size justification

Sample size calculation is based on identifying high FCR in partners. A database with 740 PCa survivors was available for partner invitation (exact number of partners unknown). Assuming an equal proportion of high FCR in cancer survivors and partners, the estimated proportion of partners with high FCR is set to 37% (range 34%-40%) [10,25]. To measure this proportion in current exploratory study with a 7% margin of error, we estimate that we will need approximately 173 partners to complete the questionnaires.

Respondents and procedure

The only eligibility criterion was that the partner was identified as being in committed relationship with a disease-free PCa survivor. Partners were invited to participate via a letter from the treating urologist that was sent between June and August 2013 to PCa survivors listed in an existing database. This database included 740 PCa survivors who were curatively treated between 1992 and 2012 at

the sites' Department of Urology. As it was unknown how many PCa survivors were in a committed relationship, all were asked if they and (if applicable) their current partner would be willing to participate in a questionnaire study. Therefore, it was not possible to ascertain exact response rates for partners because they were not contacted directly for confidentiality reasons. Results from the PCa survivor study have already been reported elsewhere (their response rate was 43%; for more details, see Van de Wal et al) [10].

By having the partner return a participation form, 311 indicated willingness to participate and 75 refused participation. Reasons for nonparticipation are displayed in Figure 1. Questionnaires were completed and returned by 219 partners. Because of incompleteness (<50% competed, n=8), false inclusion (PCa survivor not disease free, n=12) or survivor disease status unknown (n=31), 51 questionnaires were excluded from analysis resulting in n=168. Ethical approval was given by the Medical Ethics Committee, Radboud university medical center.

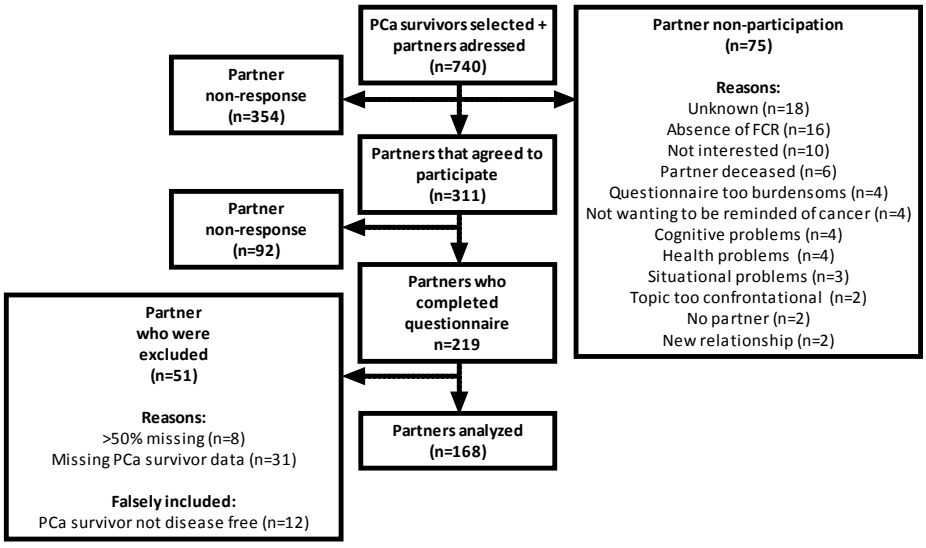


Figure 1. Flow diagram

Measures

Demographics and clinical characteristics of partners

Variable selection was guided by the theoretical model of FCR by Lee-Jones et al [12] plus past literature. Partner demographics (age, education, children [yes/no], and years as a couple) and the variable cancer history were gathered by self-report. Gender was not asked. Educational level was operationalized as lower

(elementary school and/or lower secondary education), secondary (general secondary education and intermediate vocational schooling), or tertiary (higher vocational schooling and/or university).

Partners of prostate cancer survivor information

Partners of prostate cancer survivors' information was retrieved from an existing dataset and linked to partner information in the current study. Survivor information included clinical characteristics (treatment modality, time since diagnosis and surgery) and demographics (age, education, and children [yes/no]). Furthermore, survivors' Cancer Worry Scale (CWS) scores were also available.

Fear of cancer recurrence

The FCR scores (measured by the CWS) were available for both PCa survivors and partners. The PCa survivors had completed the original CWS26 in a previous study [10], whereas partners completed a modified version in the current study. For partners, the wording of the original 8-item CWS was adjusted to make the questionnaire more suitable for their situation. For instance, the original item "How often have you thought about your chances of getting cancer (again)?" was changed to "How often have you thought about the chances of your partner getting cancer (again)?" Responses to all items were provided on a 4-point Likert scale ranging from "never" to "almost always". Scores range from 8 to 32, a higher score indicating more worries about a recurrence. A CWS score of ≥14 was found to differentiate between low and high FCR in breast and colorectal cancer survivors (sensitivity 77%/86%, specificity 81%/87%); however, a cutoff point of ≥13 was found optimal for making this differentiation in PCa survivors (sensitivity 86%, specificity 84%) [10,25,27]. The modified CWS has not been validated in partners of cancer survivors yet. To detect high FCR in (female) partners, two options to define high FCR in this group were possible. The first was using the validated CWS cutoff point of ≥13 that was found for PCa survivors. However, research in couples coping with chronic diseases has shown that women report more burden regardless of whether they are the patient or caregiver [28,29]. This suggests that there is a gender rather than role effect (i.e. patient versus partner) whereby women experience more burden or distress than men. Therefore, it seemed more logical to use the validated female breast cancer survivor cutoff score of CWS ≥ 14, rather than the cutoff for male PCa patients. In the current study, reliability of the CWS was sufficient for both PCa survivors and partners (α = 0.88 and 0.87). Incomplete items for the CWS (5%, n=9) were imputed using mean substitutions.

Health-related quality of life in partners

The HRQoL in partners was assessed using the RAND-36 [30]. The RAND-36 data were not available for survivors. The RAND-36 measures 4 physical health concepts and 4 mental health concepts: physical functioning, role limitations caused by physical health problems, pain, general health perceptions, emotional well-being, role limitations caused by emotional problems, social functioning, and energy/vitality. The internal consistency of subscales ranged from α=0.80 to 0.90 in the present sample. All scale scores were transformed linearly to a 0 (worst health) to 100 (best health) range. Missing data were handled according to the scoring manual that recommends use of mean substitution for handling of missing data [31]. If more than 50% of the items were missing on a subscale, the subscale score was not computed and was regarded as missing. The RAND-36 has sufficient psychometric properties whereby the alpha values for the subscales vary between 0.71 to 0.92 and for the test-retest reliability between 0.58 to 0.82 over a 2-month period [30,31]

Statistics

SPSSv20 was used to analyse the data. Descriptive statistics are provided as a frequency breakdown of categorical variables and medians (or means) with dispersion statistics for continuous variables. Unless otherwise specified, all analyses were tested at ≤0.05 level of significance. Mean levels of FCR were computed for partners and survivors and compared with t tests. Associations between survivors' and partners' mean CWS scores were explored using Pearson correlation. For all subsequent analyses, the CWS cutoff score was used to group partners according to low or high FCR (low≤13; high≥14). Chi-square tests were used to assess differences in proportions of high FCR between partners and survivors. A multiple linear regression analysis (enter method) of age at survey, partner (yes/no), cancer history (yes/no), education (dummy coded with lower education as the referent), children (yes/no), time since diagnosis, treatment modality, and survivors' CWS score on partner FCR was conducted. Differences in HRQoL between partners with low vs high FCR were compared with multivariate analysis of variance.

RESULTS

Participant characteristics

Demographics and clinical characteristics of partners and PCa survivors are shown in Table 1. A total of 168 partners of PCa survivors participated. Partners had a median age at survey of 67.4 years (range 40-86) and PCa survivors 70.1 years (range 54-89). Survivors were on average 7.5 years postdiagnosis (range 0.9-20). Couples had been together an average of 3 years (range 8-57). Twenty-two partners (13%) reported being examined with cancer in the past (mostly breast cancer; 41%).

Table 1. Demographics (n=168 partner-patient dyads)

	Partners, n (%)	PCa survivors, n (%)
Age at survey		
Median (range)	64.7 (40-86)	70.1 (54-89)
Education		
Lower	94 (56)	35 (24)
Secondary	46 (27)	40 (27)
Tertiary	28 (17)	70 (48)
Children		
Yes	155 (92)	151 (94)
No	14 (8)	9 (6)
Years a couple		
Median (range)	43.0 (8-57)	n.a.
History of cancer		
Yes	22 (13)	174 (100)
No	147 (87)	n.a.
Time since diagnosis (years)		
Median (range)	n.a.	7.5 (0.9-20.0)
Time since surgery (years)		
Median (range)	n.a.	5.9 (0.8-19.2)
Treatment modality		
Surgery only	n.a.	126 (75)
Surgery + RT	n.a.	41 (25

PCa = prostate cancer; RT = radiotherapy; n.a. = not applicable.

The prevalence of high FCR in partners and PCa survivors

Partners' mean rating of FCR was 12.6 (SD=3.5), which is similar to mean levels of FCR reported by PCa survivors, M=12.0 (SD = 3.8), t=−1.465, p=0.144, 95% confidence interval (CI) [−1.366 to 0.200]. A significant moderate positive correlation was found between partners' and survivors' mean levels of FCR (r=0.44, p<0.001).

When using a CWS cutoff score of ≥13 for PCa survivors and the more conservative female breast cancer survivor cutoff score of ≥14 for partners, no significant difference in the percentage of high fearful survivors (38%) or partners (35%) was found, $\chi 2(1, n=326) = 0.372$, p=0.542. Fifty-seven of the high fearful partners, compared to 28% of the low fearful partners, were in a relationship with a high fearful PCa survivor, $\chi 2(1, n=168) = 13.084$, p<0.001. Twenty-one percent of the couples consisted of both a survivor and partner with high FCR.

Further exploratory analysis using the same cutoff for both (CWS≥13) found significantly more partners reported high FCR (49% partners vs 38% survivors, p=0.03).

Demographic and clinical associates of high FCR (CWS≥14) in partners

The overall model for regression was significant (p<0.001) and explained 21% (R^2) of partner FCR. Only higher survivor FCR (β 0.310; p<0.001) and younger age of the partner (β −0.304; p=0.008) were significantly associated with higher FCR in partners (Table 2).

The HRQoL correlates of FCR in partners

Compared to partners with low FCR, partners with high FCR (CWS≥14) scored significantly worse on social functioning, emotional role functioning, mental health, vitality, and general health (Table 3). Compared to scores of a normative female population (Table 3) partners with high FCR reported significantly worse social functioning and general health (both p<0.05).

Table 2. Regression analysis of factors associated with partner FCR (n=159)

Variable	B	SE(B)	β	*t*	Sig. (p-value)
Partner variables					
Age at survey	-0.129	0.048	-0.295	-2.706	0.008*
Years a couple	0.045	0.033	0.140	1.368	0.173
Cancer history (yes/no)	0.220	0.729	0.022	0.302	0.763
Education secondary vs. lower	-0.749	0.600	-0.096	-1.249	0.214
Education tertiary vs. lower	-1.212	0.714	-0.134	-1.698	0.092
Children (yes/no)	-0.465	1.032	-0.037	-0.450	0.653
Survivor variables					
Time since diagnosis	0.043	0.060	0.064	0.719	0.477
Treatment modality	0.827	0.594	0.106	1.392	0.166
CWS score survivor	0.301	0.075	0.304	3.986	<0.001**
R^2	0.21				
F	4.324	P<0.001			
ΔR^2	0.159				

CWS = Cancer Worry Scale; *p<0.05 and **p<0.001.

Table 3. Health-related quality of life in partners with high FCR vs. partners with low FCR and a normative population

SF-36 domains	Low FCR (n=103) Mean (SD)	High FCR (n=53) Mean (SD)	*p*	Normative sample [a] Mean (SD)	*p*
Physical functioning	81.8 (18.9)	76.7 (24.8)	0.151	80.7 (23.6)	0.260
Social functioning	88.5 (16.8)	77.6 (19.1)	**<0.001****	68.1 (20.9)	**0.003****
Physical role functioning	75.7 (37.3)	71.7 (38.6)	0.529	78.3 (36.5)	0.207
Emotional role functioning	88.4 (27.9)	76.1 (37.8)	**0.023***	82.5 (33.5)	0.185
Mental health	82.0 (12.0)	74.0 (13.5)	**<0.001****	75.5 (18.9)	0.571
Vitality	71.8 (14.5)	66.4 (16.8)	**0.038***	66.3 (19.6)	0.971
Pain	84.2 (19.7)	81.4 (21.8)	0.428	80.0 (25.4)	0.696
General health	70.0 (17.0)	63.9 (20.1)	**0.042***	71.5 (21.8)	**0.014***

[a] Normative sample, Dutch female general population (n=691) RAND-36 manual [31]; *p<0.05 and **p<0.001.

DISCUSSION

This study demonstrated that FCR is not restricted to cancer survivors but affects partners as well. Amongst partners, who were on average 7.5 years post-survivor diagnosis, approximately one-third (35%) scored above the cutoff for high FCR.

Using the conservative CWS cutoff score to define high FCR, the proportion of high fearful partners in the current study is lower than reported by Zimmermann et al [16] where 51% of partners of PCa survivors (n=24) scored above the cutoff for clinical fear of progression. Reasons for differences in percentages of high FCR could be that the studies differed in respect certain partner characteristics, for instance, our sample did not include partners of survivors who had experienced a recurrence. Also, different questionnaires were used and the sample by Zimmermann et al [16] was relatively small, which makes it hard to generalize their findings. Our finding that even 7.5 years after diagnosis that a number of partners continue to experience high FCR is concerning and indicates that FCR is not restricted to the period around disease and treatment. The Dutch prostate cancer guideline advises semi-annual or annual hospital follow-ups up to 5 years postdiagnosis.32 This, together with the fact that partners do not always join the patient during medical consultations, makes high FCR in partners a problem that can remain undetected, especially in the period beyond 5 years postdiagnosis.

Partners reported a mean CWS score of 12.6. As there is no comparison data available of healthy persons or partners of cancer survivors, we compared it with the mean CWS score (12.4) found amongst family members of patients with Lynch Syndrome (HNPCC) and found no significant difference [26]. In accordance with previous studies and our hypothesis, we found that equal mean levels of FCR were reported between PCa survivors and their partners. For instance, Cohee et al [19] reported equivalent mean FCR scores between young breast cancer survivors and male partners. Three studies that have addressed FCR in caregivers (partners and relatives combined) showed equal mean levels of FCR between patients and caregivers [20] or reported that caregivers experienced higher levels of FCR [17,18]. Furthermore, in our study, partners with high FCR were more often partnered with a high fearful survivor than partners with low FCR. Also, there was a significant moderate correlation between PCa survivors' and partners' FCR. Overall, this study provides early evidence that high FCR is not only a common problem amongst partners but also that it is related to survivors' FCR as well. Future studies could therefore use dyadic approaches for a more in-depth analysis of patient-partner FCR.

We identified demographic and clinical factors associated with higher FCR in partners. Survivor FCR was the strongest significant contributor to partner FCR, further contributing to the evidence that FCR is a dyadic concern. The only other significant predictor was partners' younger age, which is in line with our hypothesis. Mellon et al [17] also found that younger age in caregivers was related to elevated FCR levels in caregivers. Reasons why a younger age has been linked to higher FCR are still speculative. It could be that those who are younger experience a greater life disruption caused by cancer. Those who are older may have had more exposure to stressful life events leaving them more resilient to FCR [33]. However, Cohee et al [19] did not find an association between age and FCR in male partners of young breast cancer survivors. In the latter study, the only demographic characteristic significantly related to higher FCR was lower education. Regarding survivors' time since diagnosis and treatment modality, we did not find a significant association with partner FCR. Our results indicate that partners experience FCR at different stages of the cancer continuum, directly after cancer treatment but also in the long-term cancer survivorship phase (>10 years post-survivor diagnosis). Because of an insufficient number of published studies, there is no clear consensus on which demographic or patient factors, except for a younger age, strongly contribute to partner FCR. This remains an important topic for future studies to address.

Finally, the relationship between high FCR in partners and their HRQoL was explored. Compared to HRQoL scores found in the Dutch healthy female population, those with high FCR scored significantly lower on social functioning and general health whereas all domain scores for those with low FCR were equal to those by the healthy norm population [31]. This is in line with our expectations and corroborates the results of many previous studies amongst cancer survivors that reported an association between high FCR and poorer emotional wellbeing [9,10,27]. One study [20] reported higher caregiver FCR to be related to poorer mental health. We did not find any differences in physical (role) functioning or pain between partners with low or high FCR.

Our results have important implications for clinical practice because they demonstrate that FCR is a significant concern for many partners of PCa survivors. A subgroup of partners might benefit from interventions designed to help them manage FCR. Most interventions or supportive care for partners of PCa survivors have focused on emotional distress (in which FCR is sporadically addressed) and sexual intimacy [34-36]. To date, none have focused exclusively on FCR in partners (or couples). In a review by Wooten et al [34], the efficacy of psychosocial interventions for the well-being of PCa survivors' partners remained inconclusive, although psycho-educational interventions and cognitive

behavioural interventions showed some promising results. As partners often have unmet needs in multiple areas, tailored generic interventions with multiple targets (eg, sexual intimacy, FCR) might be more suitable than a symptom-specific intervention.

Also, there is limited but growing evidence that FCR interventions for cancer survivors are a promising approach in managing high FCR [37,38] and it would be interesting to see if these might be adapted for treatment of partners with high FCR. Future studies should delineate the most appropriate methods to offer high fearful partners help with FCR.

Several limitations of this study warrant attention. Firstly, because of the cross-sectional design, causality and directionality cannot be implied. Prospective research is needed to identify the longitudinal trajectory of FCR in partners over time. Secondly, in the study information, we asked all partners to participate regardless of level of FCR. Unfortunately, one of the most common reasons for partner nonparticipation (21%) was no interest to participate because of absence of FCR. The percentage of partners experiencing high FCR could therefore be overestimated because of self-selection bias. On the other hand, there were also some partners who declined study participation because they perceived it as too confronting. Thirdly, it was also unknown (1) how many survivors invited their partners to participate and (2) how many survivors had a partner. Therefore, the participation rate of partners could not be precisely calculated. Nonparticipation bias has been found to be a problem in other couple-based and partner studies [39,40]. Finally, while we assume most partners to be female, gender was not explicitly asked.

The aforementioned factors limit the generalizability of our findings. As there are currently no validated questionnaires available to assess FCR in partners of cancer survivors, we chose to use an adapted version of the Dutch CWS to measure FCR and decided (on theoretical grounds) to define high FCR with the more conservative score (≥14) on this instrument. Nevertheless, we encourage the development and validation of strategies to identify partners (and caregivers) with high FCR who could potentially benefit from additional supportive care and/or intervention.

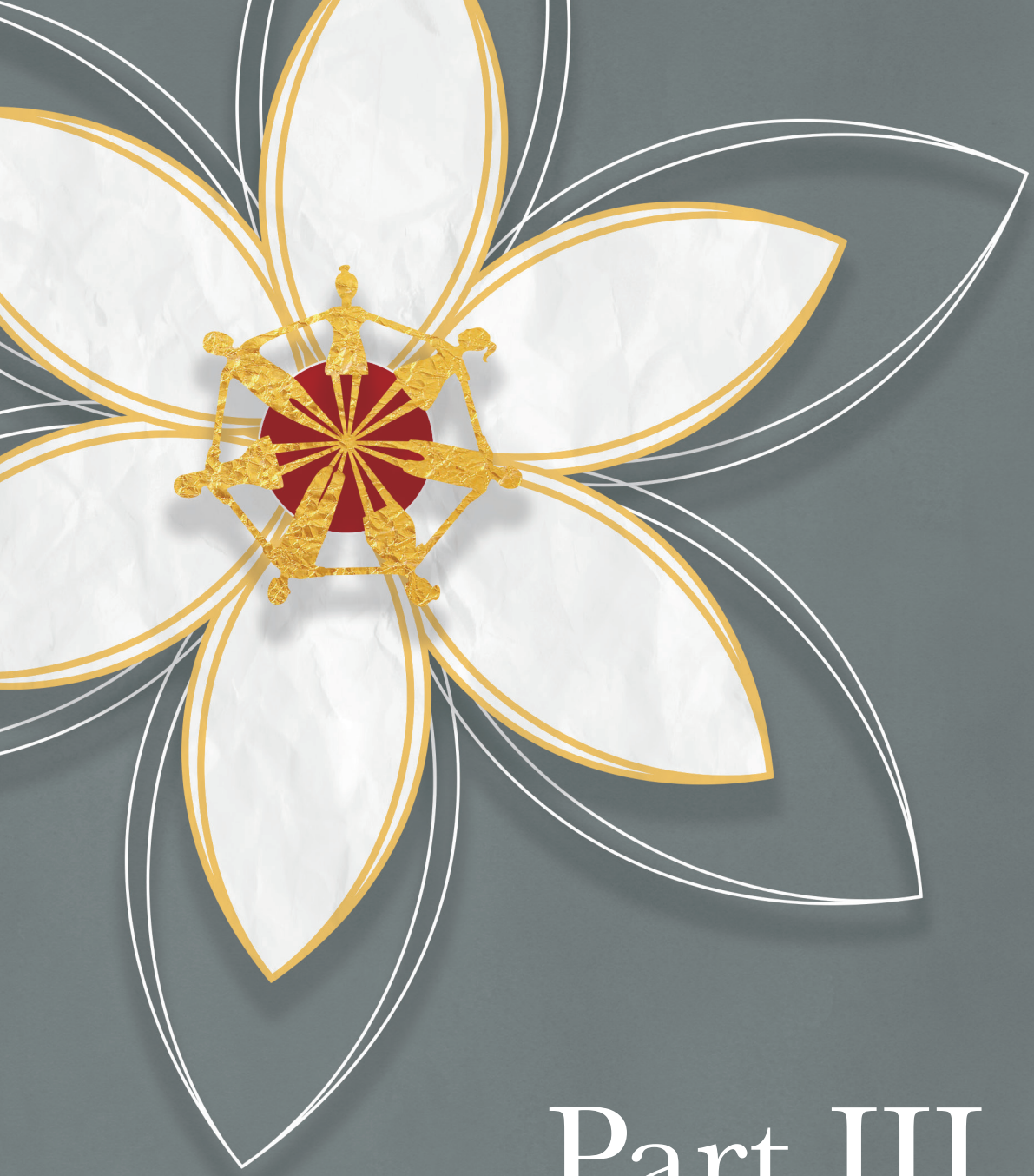
In conclusion, findings from this study illustrate that FCR is a significant concern for partners of PCa survivors. Partners with high FCR reported a worse mental and general health when compared with those who experienced low FCR. Our findings support the need for increased awareness of the presence of FCR in partners and better methods of screening for high FCR in partners (and caregivers). Furthermore, as partners with high FCR may benefit from help in managing their fears, more research on possible partner or couple interventions is encouraged. Clinical health professionals should be aware that FCR is not solely a patient affair but a problem that affects partners as well.

REFERENCES

1. Girgis A, Lambert SD. Caregivers of cancer survivors: the state of the field. Cancer Forum. 2009;33:167-171.
2. Pitceathly C, Maguire P. The psychological impact of cancer on patients' partners and other key relatives: a review. Eur J Cancer. 2003;39(11):1517-1524.
3. Harden JK, Sanda MG, Wei JT, et al. Partners' long-term appraisal of their caregiving experience, marital satisfaction, sexual satisfaction, and quality of life 2 years after prostate cancer treatment. Cancer Nurs. 2013;36(2):104-113.
4. Hagedoorn M, Buunk BP, Kuijer RG, Wobbes T, Sanderman R. Couples dealing with cancer: role and gender differences regarding psychological distress and quality of life. Psychooncology. 2000;9:232-242.
5. Hagedoorn M, Sanderman R, Bolks H, Tuinstra J, Coyne JC. Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. Psychol Bull. 2008;134:1-30.
6. Eton DT, Lepore SJ, Helgeson VS. Psychological distress in spouses of men treated for early-stage prostate carcinoma. Cancer. 2005;103:2412-2418.
7. Couper JW, Bloch S, Love A, Duchesne G, Macvean M, Kissane DW. The psychosocial impact of prostate cancer on patients and their partners. Med J Aust. 2006;185:428-432.
8. Lebel S, Ozakinci G, Humphris G, et al. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer. 2016;24(8):3265-3268.
9. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013;7:300-322.
10. Van de Wal MA, van Oort I, Schouten J, Thewes B, Gielissen MFM, Prins JB. Fear of cancer recurrence in prostate cancer survivors. Acta Oncol. 2016. https://doi.org/10.3109/0284186X.2016.1150607
11. Butler LD, Field NP, Busch AL, Seplaki JE, Hastings TA, Spiegel D. Anticipating loss and other temporal stressors predict traumatic stress symptoms among partners of metastatic/recurrent breast cancer patients. Psychooncology. 2005;14:492-502.
12. Lee-Jones C, Humphries G, Dixon R, Hatcher M. Fear of cancer recurrence— a literature review and proposed cognitive formulation to explain the exacerbation of fears. Psychooncology. 1997;6:95-105.
13. Savard J, Ivers H. The evolution of fear of cancer recurrence during the cancer care trajectory and its relationship with cancer characteristics. J Psychosom Res. 2013;74(4):354-360.
14. Lebel S, Tomei C, Feldstain A, Beattie S, McCallum M. Does fear of cancer recurrence predict cancer survivors' health care use? Support Care Cancer. 2013;21:901-906.
15. Fisher A, Beeken RJ, Heinrich M, Williams K, Wardle J. Health behaviours and fear of cancer recurrence in 10 969 colorectal cancer (CRC) patients. Psychooncology. 2016; epub ahead of print
16. Zimmermann T, Herschbach P, Wessarges M, Heinrichs N. Fear of progression in partners of chronically ill patients. Behav Med. 2011;37:95-104.
17. Mellon S, Kershaw TS, Northouse LL, Freeman-Gibb L. A family-based model to predict fear of recurrence for cancer survivors and their caregivers. Psychooncology. 2007;16:214-223.

18. Hodges JH, Humphris GM. Fear of recurrence and psychological distress in head and neck cancer patients and their carers. Psychooncology. 2009;18:841-848.
19. Cohee AA, Adams RN, Johns SA, et al. Long-term fear of recurrence in young breast cancer survivors and partners. Psychooncology. 2015. https://doi.org/10.1002/pon.4008
20. Kim Y, Carver CS, Spillers RL, Love-Ghaffari M, Kaw CK. Dyadic effects of fear of recurrence on the quality of life of cancer survivors and their caregivers. Qual Life Res. 2012;21(3):517-525.
21. Janz NK, Li Y, Beesley LJ, et al. Worry about recurrence in a multi-ethnic population of breast cancer survivors and their partners. Support Care Cancer. 2016;24(11):4669-4678.
22. Turner D, Adams E, Boulton M, et al. Partners and close family members of long-term cancer survivors: health status, psychosocial wellbeing and unmet supportive care needs. Psychooncology. 2013;22:12-19.
23. Girgis A, Lambert SD, McElduff P, et al. Some things change, some things stay the same: a longitudinal analysis of cancer caregivers' unmet supportive care needs. Psychooncology. 2013;22:1557-1564.
24. Koch L, Jansen L, Brenner H, Arndt V. Fear of recurrence and disease progression in long-term (≥5 years) cancer survivors—a systematic review of quantitative studies. Psychooncology. 2013;22:1-11.
25. Custers J, van den Berg SW, van Laarhoven HW, Bleiker EM, Gielissen MF, Prins JB. The cancer worry scale: detecting fear of recurrence in breast cancer survivors. Cancer Nurs. 2014;37:E44-E50.
26. Douma KF, Aaronson NK, Vasen HF, et al. Psychological distress and use of psychosocial support in familial adenomatous polyposis. Psychooncology. 2010;19:289-298.
27. Custers J, Gielissen MF, Jansen SH, de Wilt JH, Prins JB. Fear of cancer recurrence in colorectal cancer survivors. Support Care Cancer. 2016;24(2):555-562.
28. Coyne & Fiske. Couples coping with chronic illness. In: Akarnatsu TJ, Crowther JC, Hobfoll SC, Stevens MAP, eds. Family Health Psychology. Washington, DC: Hemisphere; 1992:129-149.
29. Lyons RF, Sullivan MJL, Ritvo PG, Coyne JC. Relationships in Chronic Illness and Disability. London: Sage; 1995:1995.
30. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51:1055-1068.
31. van der Zee KI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36, een handleiding. Groningen: Rijksuniversiteit Groningen, Noordelijk Centrum voor Gezondheidsvraagstukken; 1992.
32. Oncoline, Prostate Cancer. Comprehensive Cancer Centre the Netherlands: Oncoline. Dutch guideline for prostate cancer. http://www.oncoline.nl.
33. Rowland J. Developmental states and adaptation: Adult model. In: Holland J, Rowland J, eds. Handbook of Psycho-oncology: Psychological Care of the Patient with Cancer. New York: Oxford University Press, Inc; 1990:25-43.
34. Wootten AC, Abbott JM, Farrell A, Austin DW, Klein B. Psychosocial interventions to support partners of men with prostate cancer: a systematic and critical review of the literature. J Cancer Surviv. 2014;8:472-484.
35. Collins AL, Love AW, Bloch S, et al. Cognitive existential couple therapy for newly diagnosed prostate cancer patients and their partners: a descriptive pilot study. Psychooncology. 2013;22:465-469.

36. Northouse LL, Mood DW, Schafenacker A, et al. Randomized clinical trial of a family intervention for prostate cancer patients and their spouses. Cancer. 2007;110:2809-2818.
37. Smith AB, Thewes B, Turner J, et al. Pilot of a theoretically grounded psychologist-delivered intervention for fear of cancer recurrence (Conquer Fear). Psychooncology. 2015;24:967-970.
38. Lebel S, Maheu C, Lefebvre M, et al. Addressing fear of cancer recurrence among women with cancer: a feasibility and preliminary outcome study. J Cancer Surviv. 2014;8:485-496.
39. Terp H, Rottmann N, Larsen PV, et al. Participation in questionnaire studies among couples affected by breast cancer. Support Care Cancer. 2015;23:1907-1916.
40. Hagedoorn M, Hein FL, Schulz T, et al. Are patient and relationship variables associated with participation of intimate partners in couples research? Health Psychol. 2015;34(3):270-273.



Part III

Bereaved informal caregivers

Chapter 6

How did partners experience cancer patients' participation in a phase I study? An observational study after a patient's death

Simone M.C.H. Langenberg, Marlies E.W.J. Peters, Winette T.A. van der Graaf, Anke N.M. Wymenga, Judith B. Prins, Carla M.L. van Herpen

Palliative and supportive care (2016) 14 (3): 241-249

ABSTRACT

Introduction: It can be assumed that patients' participation in a phase I study will have an important impact on their partners' life. However, evaluation of partners' experiences while patients are undergoing experimental treatment and of their well-being after the patient's death is lacking. We aimed to explore partners' experience of patients' participation in phase I studies and to investigate their well-being after a patient's death.

Methods: This was an observational study conducted after the patient's death. Partners of deceased patients who had participated in a phase I study completed a questionnaire designed by us for experience evaluation and the Beck Depression Inventory for Primary Care, the Hospital Anxiety and Depression Scale, the Inventory of Traumatic Grief, and the RAND-36 Health Survey.

Results: The median age of the 58 participating partners was 58 years (range: 51–65), and 67% was female. Partners reported negative effects on patients' quality of life, but only 5% of partners regretted patients' participation. Approximately two years after the patients' death, 19% of partners scored for depression, 36% for psychological distress, and 46% for complicated grief, and partners generally scored significantly lower on social and mental functioning compared to normative comparators.

Conclusion: Although partners reported negative consequences on patients' quality of life, most did not regret patients' participation in the phase I studies. Prevalence of depression, psychological distress, and complicated grief seemed important problems after a patient's death, and these must be considered when shaping further support for partners of patients participating in phase I trials.

INTRODUCTION

Patients with cancer enrolled in a phase I trial have no remaining standard treatment options, but they are still in good enough clinical condition to receive experimental treatments. Along with a limited chance of benefit, experimental treatment may lead to significant side effects and more visits to the hospital [1]. This may burden a patient during the vulnerable end-of-life phase [2]. Critics have stated their concerns about patients' voluntariness, considering the risk/benefit ratio and the informed consent procedure for phase I oncological trials. The decision to participate will most often be a consequence of a misconception, coercion, or blurred judgment caused by the urgency of the patient's condition [3]. On the other hand, the well-informed patient is aware of the alternatives to enrolment, does not suffer from coercion, and is determined to fight their cancer no matter what the cost [4]. Regarding studies performed related to the ethical basis of experimental treatment, most take the point of view of the care professional or patient [3,5]. Since the partner may suffer due to the patient's burden during and following participation, the partner's point of view is at least as important, but usually not actively sought. There is increasing awareness that care for a patient with cancer has a significant impact on the partner's life [6,7]. They are not prepared and educated to provide specialized care for a patient with cancer during the often dynamic and protracted illness trajectory [8,9], and they have to integrate their role as caregiver into their own personal life, including their employment, household, and social life [10,6]. They can experience unmet needs while providing care, which bring on negative consequences for their general health [6,8]. As we noted that partners face special difficulties assisting the patient during experimental treatment, we retrospectively (1) explored the partner's point of view on patient participation in a phase I study and (2) determined their well-being after the patient's death, assessing depression, psychological distress, complicated grief, and health-related quality of life.

Our results could ultimately lead to improved support for partners during the phase of experimental therapy and after the death of patients. To our knowledge, this is the first study on the experience of partners of patients participating in phase I oncology trials.

METHODS

Sample and Procedures

This study was conducted between January of 2009 and July of 2010 and consisted of completion of validated questionnaires. Partners of deceased patients who participated in phase I studies at the Radboud university medical center between 2007 and 2009 were recruited. Some 74 partners were deemed eligible and were approached between six months and two years after a patient's death.

Although this study did not fall under the Medical Research Involving Human Subjects Act, the advice of the local medical ethical committee was requested, since the partners were regarded as a vulnerable group. Permission to conduct the study was obtained. For recruitment, a research nurse (MEWJP) contacted partners by telephone. Information was provided within a structured format in order to transmit the needed information most completely. Partners were asked to consider participation and were offered additional written information and time for consideration. Some gave oral informed consent instantly and agreed to receive the questionnaires, which were sent by mail, together with an enclosed return envelope. Some requested additional written information and needed further time to consider. After one to two weeks they were again contacted. If they decided to participate and gave oral informed consent, they received the questionnaires immediately. Completing the paper-and-pencil questionnaires took between 45 and 60 minutes.

Measurements

A general questionnaire was designed by us to obtain demographic characteristics and more specific details on a partner's experience during the patient's participation in a phase I study. A partner's experience was investigated using seven main questions (listed in Table 2). Answers to these questions were categorized in a multiple-choice format, using a 3-to-5-point Likert-type scale. Our questionnaire also assessed changes in the partner's personal situation due to patient illness and treatment, including financial problems, employment, relationship with the patient, and general health. We also evaluated the partner's experience regarding the patient's terminal phase and death, the personal situation after the death, including having received professional grief counselling, current marital status, housing, employment, and whether other important life events took place during the previous year.

For determination of partners' well-being during bereavement we used four validated questionnaires. The Beck Depression Inventory for Primary Care (BDI–PC) is a 7-item screening instrument for depression. The questions are extracted from the Beck Depression Inventory–II, which reflects DSM–IV criteria for major

depressive disorders. Each item has a 4-point scaling system, ranging from 0 to 3, and is scored by summing all scores for the 7 items. Higher scores indicate symptoms of depression. This instrument has a high internal consistency (Cronbach's α 0.85–0.88). For determination of cases, we used a cutoff score of 4 [11,12].

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-assessment questionnaire measuring psychological distress, with two 7-item subscales measuring anxiety and depression. Based on the current discussion, and considering the reliability of the use of the HADS subscales, only the total score was employed to measure psychological distress [13]. Total score ranges from 0 to 42. Each item is rated on a scale from 0 (not at all) to 3 (very much), with higher scores indicating higher levels of distress. This scale has been translated and validated for different age groups within the general Dutch population (Cronbach's α 0.84– 0.90). When the total score on the questionnaire is 12 or higher, manifest distress is likely [14].

The Inventory of Traumatic Grief (ITG) (Dutch version) is a validated (Cronbach's α 0.94) 29-item self-report questionnaire that measures maladaptive symptoms of grief. It is scored on a 5-point scale, ranging from 0 (never) to 4 (always). Summation of individual item scores yields an indication of the severity of maladaptive grief symptoms. A cutoff score of 39 or higher indicates complicated grief [15].

The RAND-36 Health Survey (RAND-36) is a validated 36-item questionnaire that assesses general health, well-being, and functional status on nine subscales: physical functioning, role physical, role emotional, mental functioning, social functioning, pain, vitality, health, and health changes. Subscale scores are transformed to a range from 0 to 100, with higher scores representing higher levels of functioning and health. The questionnaire is validated against a healthy random sample in the Netherlands and has been shown to be sufficient in terms of internal consistency (Cronbach's α 0.71–0.92). Scores for healthy normative comparators are documented in the Dutch version of the RAND manual [16].

Statistical Analyses

Statistical analysis was conducted using IBM SPSS statistics software (v. 20). Descriptive statistics with frequencies were employed to summarize the data obtained from the general questionnaire. To compare subgroups, a chi-squared test was utilized for categorical variables, and an independent sample t test was used for continuous variables. A one-sample t test was employed to compare mean scores for the sample on the RAND-36 with normative comparators. The significance level was set at $p<0.05$.

RESULTS

Participants

Of the 89 deceased patients who received experimental treatment between 2007 and 2009 in the Radboud university medical center, 12 lacked a partner and 3 partners were untraceable. Of the 74 deceased patients with a partner, 4 refused to participate in the study, 1 was not able to participate due to health problems, and 6 others refused without citing a clear reason. Finally, 63 partners (85%) were included, of whom 60 (81%) returned the questionnaires. Two partners returned the questionnaire without filling it out due to emotional difficulties brought on by the assessment process. Data from 58 (78%) partners were thus available for analysis. The characteristics of participating partners are given in Table 1.

Table 1. Partners' characteristics, n=58.

Age, median (IQR)	58 (51-65)
Minimum – maximum age, years	36-82
Gender, n (%)	
Male	19 (33)
Female	39 (67)
Duration marriage with patient, n (%)	
1-5 years	2 (3)
6-10 years	1 (2)
11-20 years	7 (12)
>20 years	48 (83)
Marital satisfaction, n (%)	
Exceptionally happy	30 (52)
Happier than average	23 (40)
A bit happier than average	2 (3)
Average	3 (5)
A bit-/ certainly-/ much less happier than average	0 (0)
Months from the patients' death up to receiving the completed questionnaire, median (IQR)	25 (19-28)
Minimum - maximum, months	7-45

Partner's Experiences During Patient's Treatment

Participation in a Phase I Study

The specifics of partners' experiences during patient participation in a phase I study are shown in Table 2. Some 33% of partners reported "somewhat negative effects" and 24% "negative effects" on patients' quality of life due to phase I study participation. "Some hindrance" or "hindrance" to the patient due to side effects were reported by 50 and 36% of partners, respectively. Outpatient control visits were reported "somewhat burdensome" and "burdensome" in 41 and 28% of partners, respectively. In contrast, 88% of partners supported patient participation and 41% reported positive effects on patient quality of life. Though a substantial number of partners regarded patient participation with mixed feelings (59%), only 5% deemed such participation regrettable.

Table 2. Experiences of the patients' participation in a phase I study from the partners' point of view

Question	Partners, n (%)
Before enrolment, how did you regard participation in a phase I study?	
I stood behind it	51 (88)
I had some difficulties with it	6 (10)
I did not support it	1 (2)
Did participation in a phase I study have a positive effect on your partner's quality of life?	
Yes	24 (41)
Somewhat	20 (35)
No	14 (24)
Did participation in a phase I study have a negative effect on your partner's quality of life?	
Yes	14 (24)
Somewhat	19 (33)
No	25 (43)
How do you reflect on side-effects your partner experienced, due to experimental treatment?	
He/she had hindrance due to the side-effects	21 (36)
He/she had some hindrance due to side-effects	29 (50)
He/she had hardly any side-effects	4 (7)
He/she experienced no side-effects	4 (7)

Table 2. Continued

Question	Partners, n (%)
Did you consider the extra control visits to the outpatient clinic burdensome during this period?	
Yes	16 (28)
Somewhat	24 (41)
No	18 (31)
Was participation in a phase I study according to your expectations? [a]	
Yes	28 (49)
Somewhat	22 (39)
No	7 (12)
How do you look back on your partner's participation in a phase I study?	
With good feelings	21 (36)
With mixed feelings; there were good moments	21 (36)
With mixed feeling; it was tough	13 (23)
With regrets	3 (5)

[a] One missing value

Patients' Terminal Phase

During the terminal phase (i.e., during the last weeks of life), 64% of patients were free from hospital admissions, whereas 26% of patients were admitted once and 10% more than once. Some 83% of patients died at home, 12% in the hospital, and 5% in a hospice. Satisfaction with the final farewell was reported by 76% of partners, while 17% regarded the farewell unsatisfactorily, and 7% were still not able to think about it. Op een nieuwe regel: Changes in partners' personal situation

Changes in partners' personal situation

Table 3 shows the changes in partners' personal situations due to patient illness and treatment. Of the 58 participating partners, an important number reported no changes in their employment (70%), no financial problems (89%), and no changes in their general health (85% reported the same general health compared to before the patient's illness; 74% experienced no health changes during bereavement compared to the period of patient illness).

Table 3. Changes in personal situation partner due to patients' illness.

Changes	n (%)
Employment [a]	
No changes	39 (70)
Worked less	13 (23)
Stopped working	4 (7)
Financial problems	
No problems	52 (89)
Yes, but solved	5 (9)
Yes, but not solved	1 (2)
Relationship with partner	
No change	25 (43)
We became closer	29 (50)
Became more difficult	4 (7)
General health during patients' illness/treatment compared to period before	
No change, same as before illness	49 (85)
Better than before illness	1 (2)
Worse than before illness	8 (13)
General health, at this moment compared to patients' illness trajectory	
Same	43 (74)
Better	7 (12)
Worse	8 (14)

[a] Two missing values

Well-Being After Patient Death

Depression, Distress, and Complicated Grief

The scores for depression, distress, and complicated grief are presented in Table 4. The mean scores for the total sample on the questionnaires showed no abnormalities compared to cutoff points. On an individual level, 19% of partners scored for depression, 36% for psychological distress, and 46% for complicated grief. No significant differences for gender were found. The concomitant prevalence of complicated grief and depression was 29%.

Table 4. Descriptives of validated questionnaires – mean scores and caseness on depression (BDI-PC), distress (HADS) and complicated grief (ITG)

Questionnaire	Total	Total score, mean (SD)	Total > cutoff (% of total)
Depression (BDI-PC)	58	2 (2)	11 (19)
Distress (HADS total)	58	9.5 (6.7)	21 (36)
Complicated grief (ITG)	57[a]	36.9 (18.3)	26 (46)

[a] One missing value (female partner)

Health-Related Quality of Life

The data for health-related quality of life are given in Table 5. Three outcomes are outlined herein. The mean scores of partners in the age group 35–44 years were lower than their normative comparators on all RAND-36 subscales, except for "physical functioning." The mean scores for the total sample showed that partners scored significantly higher on subscales "physical functioning" (p=0.001) and "pain" (p=0.039) compared to normative comparators. Partners scored significantly lower on subscales "social functioning" (p=0.010) and "mental functioning" (p=0.007). No significant differences for gender were found.

Table 5. Descriptive RAND-36 – mean scores for age groups and differences in sample mean scores compared to normative comparatives.

RAND-36 subscales	Total, n	Sample mean score (SD)	Normative comparatives, mean score (SD)	p-value
Physical	56	89.1 (15.7)	81.9 (23.2)	p=0.001
35-44	4	90 (13.5)	90.0 (14.4)	
45-54	17	94.7 (9.1)	79.9 (24.7)	
55-64	22	84.8 (20.2)	72.7 (24.4)	
65-75	10	90.5 (9.6)	66.7 (26.0)	
75-85	3	83.3 (24.7)	56.0 (29.7)	
Role emotional	55	81.8 (35.6)	84.1 (32.3)	p=0.637
35-44	4	33.3 (47.1)	82.2 (33.5)	
45-54	17	98.0 (8.1)	83.6 (34.1)	
55-64	22	77.3 (40.4)	90.1 (24.5)	
65-75	9	77.8 (37.3)	82.9 (33.8)	
75-85	3	100.0 (0)	73.7 (40.4)	

Female score, mean (SD)	Female > cutoff (% of total > cutoff)	Male score, mean (SD)	Male > cutoff (% of total > cutoff)
2.2 (2.1)	9 (82)	1.6 (1.6)	2 (18)
10.5 (6.9)	15 (71)	7.5 (6)	6 (29)
39.7 (18.6)	19 (73)	31.2 (16.7)	7 (27)

Table 5. Continued.

RAND-36 subscales	Total, n	Sample mean score (SD)	Normative comparatives, mean score (SD)	p-value
Role physical	55	82.3 (34.6)	79.4 (35.5)	p=0.540
35-44	4	62.5 (47.9)	82.9 (32.0)	
45-54	17	83.8 (33.0)	78.9 (37.0)	
55-64	22	86.4 (32.5)	76.5 (38.1)	
65-75	9	75.0 (43.3)	69.1 (42.5)	
75-85	3	91.7 (14.4)	60.1 (43.1)	
Social	58	79.1 (22.4)	86.9 (20.5)	p=0.010
35-44	4	68.8 (37.5)	88.0 (17.6)	
45-54	17	80.9 (20.3)	86.1 (21.8)	
55-64	23	78.8 (24.3)	86.6 (21.4)	
65-75	10	78.8 (20.5)	83.2 (23.7)	
75-85	4	84.4 (12)	82.0 (24.9)	
Mental	58	70.8 (16.2)	76.8 (18.4)	p=0.007
35-44	4	58.0 (26.4)	76.9 (18.0)	
45-54	17	75.5 (13.3)	76.7 (19.6)	
55-64	23	70.4 (15.4)	77.1 (18.7)	
65-75	10	68.0 (17.2)	75.9 (17.3)	
75-85	4	73.0 (18.3)	76.9 (14.3)	
Vital	58	63.9 (17.9)	67.4 (19.9)	p=0.139
35-44	4	48.8 (21.4)	67.1 (18.9)	
45-54	17	63.5 (19.7)	67.5 (20.3)	
55-64	23	64.1 (16.6)	67.0 (21.3)	
65-75	10	68.5 (13.1)	64.2 (22.0)	
75-85	4	67.5 (24.7)	60.1 (21.3)	

Table 5. Continued.

RAND-36 subscales	Total, n	Sample mean score (SD)	Normative comparatives, mean score (SD)	p-value
Pain	58	85.5 (21.7)	79.5 (25.6)	p=0.039
35-44	4	80.6 (32.3)	83.8 (21.7)	
45-54	17	92.4 (18.3)	80.5 (26.7)	
55-64	23	82 (24.1)	74.7 (25.0)	
65-75	10	89 (16.6)	74.8 (28.0)	
75-85	4	73 (20.4)	72.0 (30.3)	
Health	58	71.9 (20.9)	72.7 (22.7)	p=0.771
35-44	4	52.5 (29.0)	74.0 (20.7)	
45-54	17	79.7 (19.2)	71.6 (23.0)	
55-64	23	66.5 (21.3)	64.4 (22.2)	
65-75	10	76.5 (16.3)	60.1 (23.9)	
75-85	4	77.5 (14.4)	59.0 (21.2)	
Health change	58	55.6 (22)	52.4 (19.4)	p=0.272
35-44	4	50.0 (35.4)	55.4 (17.7)	
45-54	17	58.8 (19.6)	51.9 (19.8)	
55-64	23	51.1 (21.9)	48.7 (15.4)	
65-75	10	67.5 (20.6)	46.8 (20.5)	
75-85	4	43.8 (12.5)	45.1 (18.7)	

Personal Situation and Care After Patients' Death

Professional help for grief was received by 31% of partners, of whom 50% scored for complicated grief. A general practitioner was most often consulted (56%), followed by a psychologist (22%), a vicar (22%), a welfare worker (17%) and/or specialized bereavement support (17%). Satisfaction with grief-related care was reported by 44% of partners, 44% was neutral, and 11% were not satisfied. Table 6 presents partners' personal situation after a patient's death. Of the bereaved partners, 21% had a new relationship (men significantly more often than women; $p<0.01$).

Table 6. Partners' personal situation after patients' death.

Personal situation	n (%)
Marital status	
New partner total	12 (21)
Male	8 (67)
Female	4 (33)
No new partner total	46 (79)
Male	11 (24)
Female	35 (76)
Current employment [a]	
Paid work	38 (66)
Unpaid work	3 (5)
Housekeeper	19 (33)
No work	6 (10)
Sickness Benefits Act	3 (5)
Voluntary work	3 (5)
Housing	
Single	34 (59)
Single, living with children	16 (28)
With new partner	3 (5)
Removal to parents/children/other family members	5 (8)
Important life-events last year [a]	44 (76)
New employment	6 (14)
Retirement	2 (5)
Wedding child	2 (5)
Becoming grandparent	12 (27)
Illness of beloved (other than patient)	16 (36)
Death of beloved (other than patient)	22 (50)
Removal	3 (7)
Other	11 (25)

[a] More than one answer per partner possible

DISCUSSION

To the best of our knowledge, this is the first study to report on partners' experiences of patients' participation in a phase I study. A substantial number of partners reported that participation went according to their expectations, and they did not regret the patient's participation, though they reported hindersome side effects, burdensome augmentation of visits to the outpatient clinic, and negative effects on patient quality of life. These findings may expand on the criticism of phase I study participation at the end of life in the literature [3], and may also contribute to our ability to provide partners more information on what a patient's participation might imply for that partner, since experimental treatment has consequences for partners as well.

Depression, psychological distress, and complicated grief are frequently noted during bereavement [17]. Their prevalence in this sample was 19, 36, and 46%, respectively. The incidence of complicated grief reported in other studies in general populations is 2.4% in Japan, 3.7% in Germany, and 4.8% in the Netherlands, with a mean duration of bereavement of 13.3 years, 10 years, and 6.7 months, respectively [18-20]. For the significant others of deceased patients who suffered from cancer, the prevalence of complicated grief ranges between 18 and 40% [21-23]. In addition, the prevalence of complicated grief in bereaved individuals diminished over time in one study, with a decline from 40% at 6 months to 27% at 18 months [21]. A possible explanation for the relatively high incidence of complicated grief in our sample might be found in the combination of (1) the spousal relationship, (2) caring for the patient at the end of life (since most patients in this sample died at home), and (3) loss of another person in their inner circle, which was the case for 50% of our partners. These three factors have been identified as risk factors for complicated grief [24,23,25]. It can also be considered whether the reported high marital satisfaction contributed to more problems during bereavement.

Symptoms of complicated grief are closely related to symptoms of depression and psychological distress [25]. Their coincidence is frequently found, as is worsening of depressive symptoms due to complicated grief [17,25]. In our sample, the prevalence of depression was 19% about 2 years after the patient's death, which is high comparable to another study with 11% moderate to severe depression within bereaved family cancer caregivers at 18 months following loss [21]. Though the compared studies for depression and complicated grief employed different measurement tools at different timepoints with different sample characteristics, our findings emphasize that the psychological problems of caregivers during a patient's treatment and during bereavement merit more attention. Moreover, according to the definition of the World Health Organization [26], palliative care includes support

for family members and bereavement care. However, no consensus has been reached on the amount of support for the wide range of difficulties in a patient's terminal phase and during bereavement [21]. With regard to the number of partners with complicated grief receiving professional help after a patient's death, this was only 50% in our sample, and the help they received was scattered.

Our study can promote the consideration of depression, psychological distress, and complicated grief as three important aspects that need to be assessed in the partners of cancer patients with respect to participation in experimental treatment trials. Further research should focus on the extent to which experimental treatment can contribute to the severity of depression, psychological distress, and complicated grief experienced by partners.

On our questionnaire, a substantial number of partners reported stable general health during the patient's treatment and following their death. This was supported by a general health-related quality of life assessment. The mean scores for the total sample were significantly higher on physical functioning and pain when compared to normative comparators. This might be explained by having to confront the patient's physical limitations due to their illness and treatment. As a consequence they might value their physical functioning differently. Another explanation could be that partners of patients who participated in a phase I study were themselves in relatively good physical condition. One could expect that if a partner suffered from significant health problems, participation in a phase I study would not even be considered. It would be of added value to know if the partners suffered from comorbidities, something that was not assessed in our study. In contrast to the significantly higher scores for physical functioning, the significantly lower scores for social and mental functioning compared to normative comparators were remarkable. An association of these findings with the prevalence of depression and complicated grief in our sample could be an explanation, since these are associated with problems in social and mental functioning [25,17]. Whether problems related to social functioning could be a trigger for development of complicated grief and/or depression or the other way around remains unclear as a consequence of our study design.

Also with regard to our study design, it is important to consider that there is a possibility for recall bias, which can be related to the theory of cognitive dissonance. When confronted with incongruent or contradictory ideas or actions, which result in extreme mental stress, people try to reduce these conflicts with their beliefs [27]. Patients had made a decision to participate in a phase I trial, and partners most often supported them. After the patient's death, in order to reduce this dissonance, partners perhaps answer according to their beliefs: so the patient made the right decision to participate.

Considering the amount of depression, psychological distress, and complicated grief among the partners in our sample, the 78% response rate is remarkable. It emphasizes partners' willingness to help improve partner-related care during the patient's experimental treatment. The restrictions on performing studies of this kind, where delicate topics are investigated in vulnerable individuals, is common, but not always necessary, as discussed in other work [28] and supported by our study regarding response rate.

In conclusion, most partners of patients who participated in a phase I study supported their participation and did not regret it, though a significant number reported negative consequences for the patient's quality of life at the end of life. It is unknown whether our findings regarding the high incidence of depression, psychological distress, and complicated grief about two years after the patient's death are related to the experimental treatment. This will require further study and may perhaps ultimately lead to the required guidance for partners of patients participating in phase I oncological trials.

REFERENCES

1. Catt S, Langridge C, Fallowfield L, Talbot DC, Jenkins V (2011) Reasons given by patients for participating, or not, in Phase 1 cancer trials. European journal of cancer 47 (10):1490-1497. doi:10.1016/j.ejca.2011.02.020
2. Cox K (2000) Enhancing cancer clinical trial management: recommendations from a qualitative study of trial participants' experiences. Psycho-oncology 9 (4):314-322
3. Agrawal M, Emanuel EJ (2003) Ethics of phase 1 oncology studies: reexamining the arguments and data. JAMA: the journal of the American Medical Association 290 (8):1075-1082. doi:10.1001/jama.290.8.1075
4. Agrawal M, Grady C, Fairclough DL, Meropol NJ, Maynard K, Emanuel EJ (2006) Patients' decision-making process regarding participation in phase I oncology research. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24 (27):4479-4484. doi:10.1200/JCO.2006.06.0269
5. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC (2001) Quality of informed consent in cancer clinical trials: a cross-sectional survey. Lancet 358 (9295):1772-1777. doi:10.1016/S0140-6736(01)06805-2
6. Kim Y, Kashy DA, Spillers RL, Evans TV (2010) Needs assessment of family caregivers of cancer survivors: three cohorts comparison. Psycho-oncology 19 (6):573-582. doi:10.1002/pon.1597
7. Kim Y, Carver CS (2012) Recognizing the value and needs of the caregiver in oncology. Current opinion in supportive and palliative care 6 (2):280-288. doi:10.1097/SPC.0b013e3283526999
8. Williams AL, McCorkle R (2011) Cancer family caregivers during the palliative, hospice, and bereavement phases: a review of the descriptive psychosocial literature. Palliative & supportive care 9 (3):315-325. doi:10.1017/S1478951511000265
9. Given BA, Given CW, Sherwood P (2012) The challenge of quality cancer care for family caregivers. Seminars in oncology nursing 28 (4):205-212. doi:10.1016/j.soncn.2012.09.002
10. van Ryn M, Sanders S, Kahn K, van Houtven C, Griffin JM, Martin M, Atienza AA, Phelan S, Finstad D, Rowland J (2011) Objective burden, resources, and other stressors among informal cancer caregivers: a hidden quality issue? Psycho-oncology 20 (1):44-52. doi:10.1002/pon.1703
11. Beck AT, Guth D, Steer RA, Ball R (1997) Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behaviour research and therapy 35 (8):785-791
12. Steer RA, Cavalieri TA, Leonard DM, Beck AT (1999) Use of the Beck Depression Inventory for Primary Care to screen for major depression disorders. General hospital psychiatry 21 (2):106-111
13. Norton S, Cosco T, Doyle F, Done J, Sacker A (2013) The Hospital Anxiety and Depression Scale: a meta confirmatory factor analysis. Journal of psychosomatic research 74 (1):74-81. doi:10.1016/j.jpsychores.2012.10.010
14. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM (1997) A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychological medicine 27 (2):363-370
15. Boelen PA, Van Den Bout J, De Keijser J, Hoijtink H (2003) Reliability and validity of the Dutch version of the inventory of traumatic grief (ITG). Death studies 27 (3):227-247. doi:10.1080/07481180302889

16. VanderZee KI, Sanderman R, Heyink JW, de Haes H (1996) Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. International journal of behavioral medicine 3 (2):104-122. doi:10.1207/s15327558ijbm0302_2
17. Stroebe M, Schut H, Stroebe W (2007) Health outcomes of bereavement. Lancet 370 (9603):1960-1973. doi:10.1016/S0140-6736(07)61816-9
18. Fujisawa D, Miyashita M, Nakajima S, Ito M, Kato M, Kim Y (2010) Prevalence and determinants of complicated grief in general population. Journal of affective disorders 127 (1-3):352-358. doi:10.1016/j.jad.2010.06.008
19. Kersting A, Brahler E, Glaesmer H, Wagner B (2011) Prevalence of complicated grief in a representative population-based sample. Journal of affective disorders 131 (1-3):339-343. doi:10.1016/j.jad.2010.11.032
20. Newson RS, Boelen PA, Hek K, Hofman A, Tiemeier H (2011) The prevalence and characteristics of complicated grief in older adults. Journal of affective disorders 132 (1-2):231-238. doi:10.1016/j.jad.2011.02.021
21. Guldin MB, Vedsted P, Zachariae R, Olesen F, Jensen AB (2012) Complicated grief and need for professional support in family caregivers of cancer patients in palliative care: a longitudinal cohort study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 20 (8):1679-1685. doi:10.1007/s00520-011-1260-3
22. Allen JY, Haley WE, Small BJ, Schonwetter RS, McMillan SC (2013) Bereavement among hospice caregivers of cancer patients one year following loss: predictors of grief, complicated grief, and symptoms of depression. Journal of palliative medicine 16 (7):745-751. doi:10.1089/jpm.2012.0450
23. Chiu YW, Huang CT, Yin SM, Huang YC, Chien CH, Chuang HY (2010) Determinants of complicated grief in caregivers who cared for terminal cancer patients. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 18 (10):1321-1327. doi:10.1007/s00520-009-0756-6
24. Thomas K, Hudson P, Trauer T, Remedios C, Clarke D (2013) Risk Factors for Developing Prolonged Grief During Bereavement in Family Carers of Cancer Patients in Palliative Care: A Longitudinal Study. J Pain Symptom Manage. doi:10.1016/j.jpainsymman.2013.05.022
25. Simon NM (2013) Treating complicated grief. JAMA : the journal of the American Medical Association 310 (4):416-423. doi:10.1001/jama.2013.8614
26. Definition of palliative care (2010) World Health Organization. http://www.who.int/cancer/palliative/definition/en. Accessed Accessed November 5, 2014
27. Festinger L (1957) A theory of cognitive dissonance. Row, Evanston, Ill.,
28. Gysels MH, Evans C, Higginson IJ (2012) Patient, caregiver, health professional and researcher views and experiences of participating in research at the end of life: a critical interpretive synthesis of the literature. BMC medical research methodology 12:123. doi:10.1186/1471-2288-12-123

Chapter 7

Summary

SUMMARY

A cancer diagnosis is a stressful event for patients and their families. Informal caregivers play an important role for patients diagnosed with and treated for cancer. Partners and other informal caregivers of a patient with cancer can experience a wide range of psychological problems which may impact their emotional health. The aim of this thesis was to gain more knowledge about informal caregivers' functioning of a patient on active cancer treatment (part 1), after completion of treatment (part 2), or after a patients' death (part 3). The final chapter summarizes and discusses all previous chapters. Moreover, it describes practical implications for clinical practice and formulate recommendations for future research. Table 1 shows an overview of the examined constructs used in the studies in this thesis. Table 2 to 5 shows an overview of mean and cutoff scores of burden and distress.

PART 1:
CARING FOR A PATIENT DURING THE TREATMENT PHASE

Informal caregivers of patients treated with curative intent

Concomitant chemoradiotherapy in locally advanced head and neck cancer (LAHNC) challenges both patients and their informal caregivers. Patients often experience fatigue, psychological distress (hereafter described as "distress") and poor health-related quality of life (HRQoL), which in turn may burden informal caregivers. In **Chapter 2,** we described the course of informal caregiver burden and fatigue in relation to the patient's fatigue, distress, and HRQoL. In addition, we identified risk factors for higher levels of informal caregiver burden and fatigue after completing chemoradiotherapy. Informal caregiver burden and fatigue peaked when patient fatigue and distress peaked, together with lowest patient HRQoL. One week after completion of chemoradiotherapy, informal caregiver burden and patients' fatigued peaked. Three months later, these increased levels returned to baseline burden and fatigue. Female partners with higher baseline burden and fatigue, caring for patients with poor HRQoL were at higher risk for increased burden. With respect to fatigue, the main risk factor for caregiver fatigue after completion of chemoradiotherapy was high levels of fatigue at baseline.

In **chapter 3**, we focused on informal caregiver burden and distress during and after completion of patients' adjuvant chemotherapy for colon cancer. We examined 1) the number of informal caregivers having higher levels of burden and distress, and the course of informal caregiver burden and distress over time, 2) risk factors for developing higher levels of burden and distress during and after treatment, 3) associations between informal caregivers' burden and distress and patients' distress, and 4) the course of informal caregivers' health-related quality of life over time and how this is associated with their own burden and distress, and with distress of the patient. Our findings showed that informal caregiver distress and burden was relatively low and reduced over time. At baseline, 27% (n=16/60) of caregivers reported clinically relevant levels of distress and 12% (n=7/58) reported high levels of burden. These percentages did not change over time. Informal caregiver burden and distress at baseline predicted their levels of burden and distress, respectively, both during adjuvant chemotherapy and three months after completion of treatment. Overall, informal caregiver burden and distress were not correlated with patient distress, with the exception of an association between informal caregiver burden and patient distress at baseline.

Informal caregivers of patients on long-term treatment

Long-term treatment with Tyrosine Kinase Inhibitors (TKIs) for Gastrointestinal Stromal Tumours (GIST) seems to be associated with burden and distress for the informal caregiver. However, details about the amount and severity of burden and distress are lacking. In **chapter 4,** we described the level of informal caregiver burden and distress during patients' long-term treatment with TKIs, and the characteristics of those informal caregivers with high levels of distress and burden compared to their counterparts with low levels of distress and low/moderate perceived burden. Overall, informal caregivers of patients treated for GIST seemed to manage well. Perceived burden and distress were low in this group and their perceived general HRQoL was good and similar to the general population. In addition, marital satisfaction was good and they did not experience discrepancies in social support. On the other hand, 51% (n=30/61) of the patients in this study reported bothersome or severe side effects of treatment and 34% (n=21/61) experienced clinically relevant levels of distress. By comparison, 10% (n=6/61) of informal caregivers reported high levels of burden and 23% (n=14/61) had clinically significant levels of distress. Patients' distress was associated with informal caregivers' distress and burden. Informal caregivers with high levels of burden reported significantly poorer mental health, less vitality, lower general HRQoL and high distress. Significantly higher levels of burden were found in non-spouses, informal caregivers of patients with more treatment-related side effects, informal caregivers who spent more hours caring, and those caring for more than one person simultaneously. In addition,

informal caregivers with high levels of distress perceived significantly more burden, lower social functioning, more role physical and emotional problems, poorer mental health, less vitality, and lower general HRQoL. Furthermore, high levels of distress were found in informal caregivers of more dependent patients and those caring for more than one person simultaneously.

PART 2:
INFORMAL CAREGIVERS OF PATIENTS AFTER TREATMENT

Informal caregivers of patients in the survivorship phase

Fear of cancer recurrence commonly affects cancer survivors. Partners of cancer survivors may also experience fear, which can impact their HRQoL. In **chapter 5,** we described 1) the rate of fear of cancer recurrence (FCR) among partners of patients with prostate cancer, 2) the relation between partners' and patients' FCR, 3) partners' demographics and survivors' clinical characteristics associated with high FCR, and 4) the relationship between high FCR and their HRQoL. Mean levels of FCR were similar between partners and survivors. Thirty-five percent (n=59/168) of partners reported high FCR compared to 38% (n=64/168) of prostate cancer survivors. Higher survivor FCR and younger partner age were significantly associated with higher partner FCR. Partners with high FCR scored significantly lower on social functioning, emotional role functioning, mental health, general health, and vitality than those with low FCR.

PART 3:
BEREAVED INFORMAL CAREGIVERS

Bereaved partners of patients treated in a phase I study

Chapter 6 describes the partners' perspective of patients' participation in an experimental, phase I clinical trial. Furthermore, we explored bereaved partners' problems in terms of depression, distress, complicated grief, and HRQoL. Partners reported negative effects of phase I trial participation on patients' HRQoL, but only 5% (n=3/58) of partners regretted the patients' participation. Approximately two years after the patients' death, 19% (n=11/58) of partners scored high for depression, 36% (n=21/58) for distress, and 46% (n=26/57) for complicated grief. In general, partners scored significantly lower on social and mental functioning compared to normative comparatives.

Table 1. Overview of examined constructs used in the studies reported in this thesis

Construct	Head&neck	Colon	GIST	Prostate	Phase I
Burden	●	●	●		
Distress		●	●		●
HRQOL		●	●	●	●
Fatigue	●	●			
Complicated grief					●
Depression					●
FCR				●	
Marital satisfaction		●	●		
Social needs		●	●		

HRQOL=health-related quality of life; FCR=fear of cancer recurrence

Table 2. Informal caregivers' burden mean scores between different studies reported in this thesis

	Time points		
Study	**T0**	**T1**	**T2**
Head and neck, mean (SD) [a]	4.1 (2.4)	4.6 (2.4)	3.2 (2.4)
Colon, mean (SD) [b]	2.9 (2.44)	2.82 (2.38)	2.04 (2.25)
GIST, mean (SD) [c]	2.4 (2.3)	-	-

[a] Time points for head and neck: T0 = prior to start chemoradiotherapy (n=56), T1 = 1 week after ending chemoradiotherapy (n=49), and T2 = 3 months after the end of chemoradiotherapy (n=45); [b] Time points for colon: T0 = baseline, before starting adjuvant chemotherapy (n=60), T1 = between the second and third cycle (n=58), T2 = three months after ending adjuvant chemotherapy (n=51); [c] GIST: cross-sectional study, one measurement point only (n=61)

Table 3. Informal caregivers' burden cutoff scores for high levels of burden

	Time points								
	T0			**T1**			**T2**		
Study	**Moderate**	**High**	**Total**	**Moderate**	**High**	**Total**	**Moderate**	**High**	**Total**
Head and neck	36%	11%	47%	63%	21%	84%	22%	11%	33%
Colon [a]	17%	12%	28%	19%	11%	29%	12%	8%	20%
GIST [b]	16%	10%	26%						

[a] Time points for head and neck: T0 = prior to start chemoradiotherapy (n=56), T1 = 1 week after ending chemoradiotherapy (n=49), and T2 = 3 months after the end of chemoradiotherapy (n=45); colon: T0 = baseline, before starting adjuvant chemotherapy (n=60), T1 = between the second and third cycle (n=58), T2 = three months after ending adjuvant chemotherapy (n=51); [b] GIST: cross-sectional study, one measurement point only (n=61)

Table 4. Informal caregivers' distress mean scores between different studies reported in this thesis

	Time points		
Study	**T0**	**T1**	**T2**
Colon, mean (SD) [a]	9.0 (6.9)	7.6 (6.3)	6.6 (7.2)
GIST, mean (SD) [b]	8.1 (5.7)		
Phase I, mean (SD)	9.5 (6.7)		
Studies cancer caregivers [1-3]	7.3 (4.3) – 17.5 (9.1)		
General population [4-6]	7.6 (6.0) – 9.8 (5.9)		

[a] Time points for colon: T0 = baseline, before starting adjuvant chemotherapy (n=60), T1 = between the second and third cycle (n=58), T2 = three months after ending adjuvant chemotherapy (n=51); [b] GIST: cross-sectional study, one measurement point only (n=61); [c] Phase I: cross-sectional study, one measurement point only (n=58)

Table 5. Informal caregivers' distress cutoff scores for clinically relevant levels of distress

	Time points		
Study	**T0**	**T1**	**T2**
Colon [a]	27%	23%	19%
GIST [b]	23%		
Phase I [c]	36%		
Studies with cancer caregivers [1]	20%		
General population [4,6]	12.6-30.2%		

[a] Time points for colon: T0 = baseline, before starting adjuvant chemotherapy (n=60), T1 = between the second and third cycle (n=58), T2 = three months after ending adjuvant chemotherapy (n=51); [b] GIST: cross-sectional study, one measurement point (n=61); [c] Phase I: cross-sectional study, one measurement point (n=58)

REFERENCES

1. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, Kuik DJ, de Bree R, Leemans CR (2007) Distress in spouses and patients after treatment for head and neck cancer. The Laryngoscope 117 (2):238-241. doi:10.1097/01.mlg.0000250169.10241.58
2. Tan JY, Molassiotis A, Lloyd-Williams M, Yorke J (2018) Burden, emotional distress and quality of life among informal caregivers of lung cancer patients: An exploratory study. Eur J Cancer Care (Engl) 27 (1). doi:10.1111/ecc.12691
3. Li Q, Lin Y, Xu Y, Zhou H (2018) The impact of depression and anxiety on quality of life in Chinese cancer patient-family caregiver dyads, a cross-sectional study. Health Qual Life Outcomes 16 (1):230. doi:10.1186/s12955-018-1051-3
4. Hinz A, Brahler E (2011) Normative values for the hospital anxiety and depression scale (HADS) in the general German population. Journal of psychosomatic research 71 (2):74-78. doi:10.1016/j.jpsychores.2011.01.005
5. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM (1997) A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychological medicine 27 (2):363-370
6. Crawford JR, Henry JD, Crombie C, Taylor EP (2001) Normative data for the HADS from a large non-clinical sample. The British journal of clinical psychology / the British Psychological Society 40 (Pt 4):429-434

Chapter 8

General discussion

GENERAL DISCUSSION

Informal caregivers and their challenges in perspective

Burden

In our studies, informal caregiver **burden** was highest for those caring for patients with head and neck cancer (HNC) (33-84%), followed by those receiving longer-term TKI treatment for GIST (26%) and those receiving adjuvant treatment for colon cancer (20-29%). Informal caregivers of patients with head and neck cancer were twice as likely to report moderate to high levels of burden (47%) compared to patients starting adjuvant treatment for colon cancer (28%) or those on long-term treatment for GIST (26%). It is known that in head and neck cancer patients' major depressive disorders are more prevalent when compared to other cancer patients [1]. This together with the intensity and side effects of concomitant chemoradiotherapy are factors that may distinguish these patients from other cancer patients and may challenge their informal caregivers more intensely. Additionally, Richardson et al. described that 19% of informal caregivers of patients with HNC suffered from a posttraumatic stress disorder (PTSD) approximately 6 months after diagnosis [2]. Risk factors associated with informal caregivers' PTSD were avoidant coping, many cancer symptoms and perception of low benefit of treatment.

Increased burden can be regarded as a normal reaction to a major stressor and the course of burden described in this manuscript could reflect adaptation to a major event in the life of an informal caregiver, i.e. burden peaked during treatment and returned to pre-treatment levels after treatment. This echoes earlier findings, as does our finding that there is a group of informal caregivers who remained burdened after ending treatment [3-5]. Distinguishing between a normal reaction, where an informal caregiver will adapt, and a situation where an informal caregiver continues to suffer from high levels of burden is challenging. To help identify those informal caregivers at risk for higher levels of burden, we studied several sociodemographic, care-related and patient-related factors previously associated with burden. We found that risk factors for burden of informal caregivers of patients treated for head and neck cancer were multidimensional; female spouses with higher baseline levels of burden and fatigue, and caring for patients with lower levels of global HRQoL seemed at higher risk for burden after the end of the intensive treatment of chemoradiotherapy. For informal caregivers of patients with colon cancer baseline burden contributed significantly to burden during and after treatment. Having higher baseline problems causing burden later on was also found in other studies [3,6]. Teixeira et al. reviewed the underlying mechanisms of burden [7]. They concluded that problem-focused coping attributes to decreased informal

caregiver burden and that emotion-focused coping is associated with higher levels of general distress and posttraumatic stress disorder symptoms. They proposed multiple avenues for informal caregiver intervention, including the facilitation of improved coping strategies, improved emotion regulation skills, self-care, and family functioning [7].

Distress

In our study with informal caregivers of patients with colon cancer, 27% of informal caregivers experienced symptoms of **distress** before patients start of adjuvant treatment. Additionally, 23% of informal caregivers of patients on long-term palliative treatment for GIST reported symptoms of distress. When comparing the mean level of distress found in our studies to the general population and informal caregivers in other studies, these were similar [8-13].

Distress can be a normal response to a major stressor in the lives of informal caregivers of patients treated for colon cancer, which, when they find ways to adapt, improve over time. Similar to burden, there is need to identify informal caregivers at risk for longer-term distress. We found that informal caregivers with higher levels of distress, cared for more dependent patients and/or more than one individual at a time. More distress is experienced when caring for a significant other has higher impact on their day-to-day schedule [8,14,15]. Additionally, baseline distress is a risk factor for longer term distress, which has also been described in other studies [8,14,15].

It is important to understand the source of informal caregivers' distress. Northouse et al. reviewed on the sources of emotional distress according to the phase of a patient's illness. These authors described that in the diagnostic phase, caregivers experience unmet needs on different aspects, uncertainty how to address patients' needs, feelings of being overwhelmed and powerless in combination with different care demands. During the treatment phase, informal caregivers lack experience and preparedness to perform (difficult) care tasks, manage juggling demands of others without help, and deal with feelings of social isolation. Furthermore, they worry about the effectiveness of patients' treatment and experience difficulties how to manage side effects [14]. We also found that informal caregivers of patients treated for GIST were more burdened and distressed when patients experienced side effects. Furthermore, patients with GIST who reported fear of cancer progression also had high levels of distress [16], which will impact the informal caregiver as well [17].

Informal caregivers' coping mechanism could play a role in adjusting to a major stressor in their lives. Perez-Ordóñez et al. described that distress of informal caregivers of patients on palliative treatment was related to dysfunctional coping (behavioural disengagement, denial, self-distraction, self-blame, substance use and venting) and they advised interventions aiming to reduce these coping

mechanisms [18]. Together with more focus on informal caregivers' coping, spiritual care deserves attention. It is known that spirituality functions as internal resource to cope with and forms a buffer for experiencing psychological distress [19]. Kim et al. found that informal caregivers who were highly spiritual, experienced less psychological distress, especially when giving care to a significant other was more challenging [19]. Selman et al. described in a qualitative study that informal caregivers have a wide range of spiritual questions and that their spiritual practices, beliefs and support from faith communities helped them cope with their role [20].

Depression and complicated grief

In our study with bereaved partners of patients who participated in a phase I study (i.e. received experimental treatment) in the last phase of their life, we found a high number of partners who experienced **distress** (36%), **complicated grief** (46%) and **depression** (19%), approximately 2 years after patients' death. Symptoms of depression are closely related to symptoms of complicated grief and their coincidence is frequently found [21,22]. Reacting to bereavement varies between individuals as well as between cultures and ethnic groups [21]. The proportions we found are higher than in other studies of partners of deceased cancer patients at this point in time and when compared to the general population and other partners of deceased patients who suffered from cancer [23-28]. We observed that spousal relationship, being mainly responsible for caring for the patient at the end of life and another recent loss of a beloved one contributed to developing symptoms of complicated grief in our study. These findings are supported by other studies [22,28,29]. Another contributing factor could be that partners in our study suffered more from complicated grief due to a more avoidant coping strategy. Teixiera et al. and Perez-Ordóñez et al. describe that there is a difference in psychological health outcomes when informal caregivers have dysfunctional coping strategies [7,18]. Furthermore, patients' low levels or even a total lack of acceptance of illness can contribute to feelings of distress in both patients and their partners, which will have influence on partners' grief process. Moreover, patients' acceptance is, amongst others, determined by the response to their illness by their relatives [30]. Continuing patients' treatment during the last phase of their lives may have interfered with partners realisation and acceptance of their forthcoming loss. This may have complicated their grief after the patient's death as well [22,31].

Exploring coping in relation to informal caregivers' depression and grief and what their spiritual care needs are when a patients is treated in a phase I experimental study could be an interesting field of future research. Selman et al. described in a qualitative study that informal caregivers gave advise to further explore their spiritual care needs and they emphasized that this is also needed during bereavement.

Health-related quality of life and fatigue

In all our studies we found that informal caregivers with more problems, like higher levels of burden, distress and/or fear of recurrence, experienced more problems in social functioning and lower levels of general health, especially lower levels of mental health. It is known that mental health is intertwined with social functioning [14,32]. Pasek et al. described in a study with informal caregivers of patients on active curative treatment for cancer that informal caregivers' sense of coherence, i.e. the degree of trust to comprehend, manage and find meaning in a challenging situation, was determined by the levels of perceived social support [30]. As informal caregivers' sense of coherence is a resource in patients' acceptance of illness, focusing on informal caregivers social functioning might benefit themselves and patients as well [30].

As part of exploration of informal caregivers' general health, we also studied fatigue. Fatigue is a complex phenomenon. We found that fatigue is an important issue among informal caregivers, as their fatigue is higher than average, especially in informal caregivers of head and neck cancer patients. We also found that fatigue before treatment is a risk factor for fatigue after end of treatment. Traa et al. found that partners with more depressive symptoms were at risk for developing higher levels of fatigue [33]. Peters et al. found that caregiver fatigue was related to informal caregiver burden when patients were on palliative treatment [34].

These findings underline that mental and physical problems are related and that it seems important when we aim to improve their general health, both mental and physical, we need to pay attention to informal caregivers' psychosocial functioning and focus on their social support system. It is known that better social support can improve the perception of burden and other mental health problems, which may also improve patients' acceptance of their illness better [4,30,32].

Fear of cancer recurrence

We found that 35% of partners of prostate cancer survivors suffered from **FCR** and that the mean levels of FCR of partner and patients were comparable. The similarity in levels of FCR is in line with other studies [35,36]. Moreover, studies reported that informal caregivers' FCR exceeded that of survivors [36,37]. We found that higher survivor FCR and younger partner age were significantly associated with higher partner FCR. Furthermore, partners with high FCR scored significantly lower on social functioning, emotional role functioning, mental health, general health, and vitality than those with low FCR. Mellon et al. described that both individual as well as dyadic factors play a role in the

development of FCR and that partners' higher level of FCR was also associated with a negative influence on their HRQoL [38]. Cohee et al. found that cognitive processing mediates experiencing social constraints and increased levels of FCR. [39] Additionally, coping mechanisms, like avoidant coping, may also play a role in developing FCR [35-37,39].

Clinical implication & future research

Recognizing, acknowledging & resources

Based on the findings described in this thesis, it is clear that caring for a patient with cancer impacts the life of the informal caregiver, with possible negative consequences for their mental and physical health. In clinical practice three aspects are important to improve informal caregivers support: 1) healthcare professionals pay more attention to informal caregivers and recognize informal caregiver problems, 2) informal caregivers acknowledge there is a problem and accept support, and 3) availability of resources to address the problems.

First, it is important that attention is paid to informal caregivers. Counselling in general about the role as caregiver must be incorporated in patient information about their cancer treatment. Knowing that there is attention for informal caregiver functioning and normalizing their burden may help them lowering the threshold to ask for support. Together with counselling informal caregivers on their new role, it is advisable to screen for informal caregivers' baseline problems, such as burden and distress. As the general practitioner serves as a family doctor and, according to the Medical Treatment Agreement Act, the general practitioner has a treatment relationship with the informal caregiver, it seems most suitable they facilitate screening and assessment what support suites the informal caregivers best. Offering support warrants healthcare professionals in the 1st line in care to join forces with healthcare professionals of the 2nd and 3rd line.

In addition to the need for increased awareness by healthcare professionals of informal caregiver functioning, it is essential that the informal caregiver acknowledges if there is a problem, and accepts support. This remains a challenge in clinical practice. Informal caregivers often have the need to see their tasks alleviated, but on the other hand perceive difficulties in delegating their tasks. Therefore, it is essential to educate informal caregivers about their role and the possible consequences this may have for their own health, and how they can balance between taking good care of the patient and themselves as well.

There is increasing knowledge that psychoeducation, supportive care/support interventions, mindfulness-based stress reduction and cognitive behavioural interventions are recommended to alleviate informal caregivers' burden [40]. Unfortunately, a Cochrane review on the effectiveness of psychosocial interventions

for informal caregivers of patients with cancer described that studies on this subject show great heterogeneity, what makes it difficult to draw general conclusions about the effectiveness of psychosocial interventions on informal caregivers' and patients' quality of life [41]. Like the current shift in personalized patient care, this seems also applicable to support of informal caregivers. There is no "one size fits all" format to address informal caregivers' problem, as their needs may range from practical to emotional. When problems do occur this warrants a multidisciplinary approach with psychologists, social workers and/or spiritual counsellors involved, depending on the source of their problem.

Future research should focus on understanding how informal caregivers with high levels of burden and distress cope with a major stressor in their life and what could buffer burden and distress. There is a clear need for spiritual care reported by informal caregivers in a palliative care setting. In a study of Selman et al. informal caregivers emphasized to focus future research on educational interventions for healthcare professionals to improve their spiritual care skills, investigate suitability of spiritual care for diverse populations, including those without religious faith, improve assessment of informal caregivers' spiritual needs, and study the impact of improved spiritual care, including during bereavement [20]. Additionally, it seems of added value to further study the positive aspect of giving care to a significant other. For a long time, it was thought that the burden and benefits were two ends of one continuum. Pendergrass et al. showed in a cross-sectional study that there is evidence that positive and negative effect of caregiving can co-occur and that the benefits of caregiving can buffer psychological distress [42]. However, there is need for longitudinal studies to further explore the possible buffering effects of caregiving informal cancer caregivers' mental and physical health on the longer term.

The current COVID-19 pandemic has a significant effect on a person's well-being and mental health, due to the measures taken, such as social distancing, self-isolation and quarantine. For informal caregivers this forms an even greater challenge as they are isolated from their social connections, and sometimes even from their loved ones, when they are admitted to the hospital [43]. As telehealth and phone check-ins are getting a more prominent place in care due to the COVID-19 pandemic, this could also be an interesting field of research to further improve informal caregiver support [43].

Validated questionnaires & cut-off points for informal caregivers

A common challenge, aside from recognizing informal caregiver problems, is objectivating these problems. As described in this thesis, the problems of an informal caregiver faces are complex and the experience of burden is multi-dimensional. There are a couple of questionnaires validated to measure informal

caregiver burden, like the Self-perceived pressure of informal care (SPPIC), the Caregiver Reaction Assessment (CRA) and The Zarit Burden Interview [44-46]. Applying these questionnaires in research delivered important information about informal caregiver functioning. However, for many other concepts and problems, such as distress, HRQoL and fatigue, there are no validated questionnaires and/or cut-off points for informal caregivers of patients with cancer. This could be an interesting field of further research, to improve the quality of studies with informal caregivers of patients with cancer. In addition, in order to interpret clinically relevant changes of problems over time, there is need for the establishment of minimally clinically important differences (MCID), which could complement assessed statistical changes. This could support further research on interpreting effects of interventions to improve informal caregivers' functioning.

Consequences of caregiving on caregivers' physical health

In our study with informal caregivers of patients treated for GIST, we did not find that informal caregivers' comorbidities were associated with high levels of burden and distress. Informal caregiver problems were especially determined by emotional challenges, which may impact physical health. Rohleder et al. found that in the year after patients' cancer diagnosis, familial caregivers experienced marked changes in neurohormonal and inflammatory processes, with increasing inflammation and dysregulation of inflammatory control over time [47]. These inflammatory processes can be involved in the development of cardiovascular disease. A study of Lee et al. showed that high caregiving burden in spouses was an independent risk factor for coronary heart disease, after controlling for a range of behavioural, social, and physical factors [48]. Comprehending the impact of the role of caregiving on informal caregivers' physical health would increase the knowledge of the caregiving experience as a whole and help in preventive informal caregiver care. Understanding the relationship between mental problems and their consequences for informal caregivers' physical health could emphasize the urge to support informal caregivers even more. Research on the physical consequences of informal caregiver problems is scarce and this could be an interesting field of future research, which could ultimately lead to ways to prevent informal caregivers' health problems.

Novel treatments

Immunotherapy is a relatively new and promising treatment modality for certain groups of patients with cancer. The treatment is in most patients well-tolerated, but when side-effects occur they can be severe and may impact the patient seriously and sometimes the result will be that treatment is not continued, with long-term

permanent organ dysfunction. [49] The ultimate goal of immunotherapy is to create a durable, long-term tumour response. There is a group of patients treated with immunotherapy having a complete response after treatment, but there remains uncertainty about what this complete response means in terms of curation. On the other side of the spectrum there is group of patients unresponsive to this treatment, which is not always clear immediately as a response to this therapy takes time. This all has impact on the patient and will most probably impact the informal caregiver as well. Although informal caregiver problems seem to be mostly determined by their own psychological functioning and coping mechanisms, and not specifically the type of cancer and/or its treatment, the impact of a treatment/toxicity seem to influence their functioning during/after treatment. How the patients' treatment with immunotherapy affects the informal caregivers could be an interesting field of further research.

CONCLUSION

Informal caregivers of cancer patients are at risk of experiencing burden, which is a multidimensional experience which can have serious general health consequences and can impact informal caregivers' functioning. There is a vulnerable group of informal caregivers with higher levels of burden and distress, especially among informal caregivers of patients treated for locally advanced head and neck cancer and bereaved partners of patients treated in phase I studies in the end-of-life phase. Furthermore, we found that baseline emotional problems and fatigue are an important risk factor for problems on the longer term, and therefore, early identification of problems seems necessary. This is a challenging task since and there is no "one-size-fits-all" approach. Educating informal caregivers on their role and the possible consequences of this role on their health needs to be implemented in clinical care of patients treated for cancer. Furthermore, supporting informal caregivers must be a team effort of healthcare professionals in the 1st, 2nd and 3rd line of care. Healthcare professionals in the 2nd and 3rd line need to recognize informal caregivers' problems and informal caregivers must acknowledge their problems in order to accept help. The general practitioner as leading physician in informal caregiver care can play a central role in facilitating and initiating informal caregiver support. Further exploration of ways to help informal caregivers of cancer patients to cope with the dynamic, stressful situation is needed.

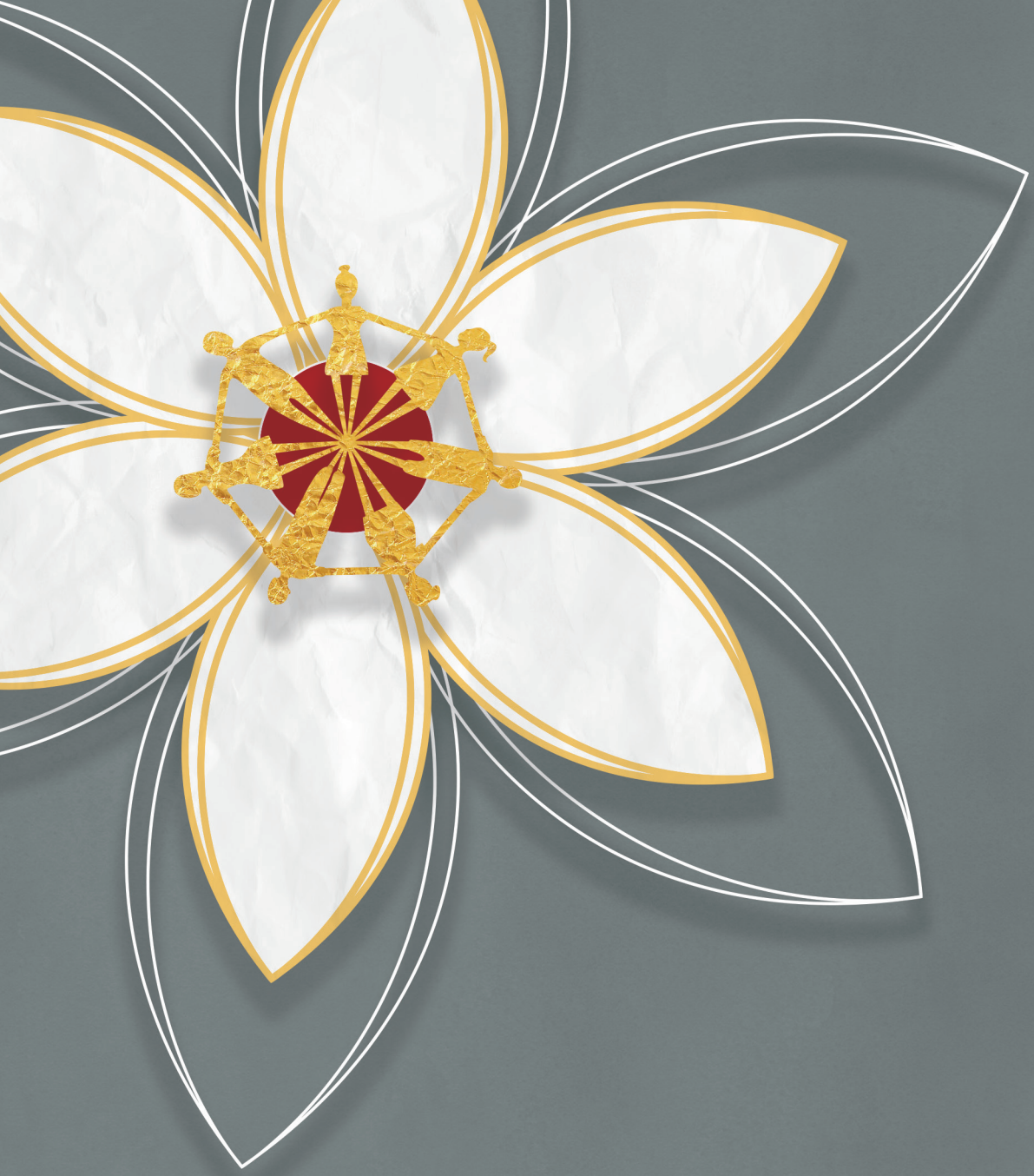
REFERENCES

1. Lydiatt WM, Moran J, Burke WJ (2009) A review of depression in the head and neck cancer patient. Clinical advances in hematology & oncology : H&O 7 (6):397-403
2. Richardson AE, Morton RP, Broadbent EA (2016) Illness perceptions and coping predict post-traumatic stress in caregivers of patients with head and neck cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 24 (10):4443-4450. doi:10.1007/s00520-016-3285-0
3. Jansen L, Dauphin S, De Burghgraeve T, Schoenmakers B, Buntinx F, van den Akker M (2019) Caregiver burden: An increasing problem related to an aging cancer population. J Health Psychol:1359105319893019. doi:10.1177/1359105319893019
4. Nightingale CL, Curbow BA, Wingard JR, Pereira DB, Carnaby GD (2016) Burden, quality of life, and social support in caregivers of patients undergoing radiotherapy for head and neck cancer: A pilot study. Chronic illness 12 (3):236-245. doi:10.1177/1742395316644305
5. Grunfeld E, Coyle D, Whelan T, Clinch J, Reyno L, Earle CC, Willan A, Viola R, Coristine M, Janz T, Glossop R (2004) Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. CMAJ 170 (12):1795-1801. doi:10.1503/cmaj.1031205
6. Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS (2014) Caregiver burden: a clinical review. JAMA : the journal of the American Medical Association 311 (10):1052-1060. doi:10.1001/jama.2014.304
7. Teixeira RJ, Applebaum AJ, Bhatia S, Brandao T (2018) The impact of coping strategies of cancer caregivers on psychophysiological outcomes: an integrative review. Psychol Res Behav Manag 11:207-215. doi:10.2147/PRBM.S164946
8. Hinz A, Brahler E (2011) Normative values for the hospital anxiety and depression scale (HADS) in the general German population. Journal of psychosomatic research 71 (2):74-78. doi:10.1016/j.jpsychores.2011.01.005
9. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM (1997) A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychological medicine 27 (2):363-370
10. Crawford JR, Henry JD, Crombie C, Taylor EP (2001) Normative data for the HADS from a large non-clinical sample. The British journal of clinical psychology / the British Psychological Society 40 (4):429-434. doi:10.1348/014466501163904
11. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, Kuik DJ, de Bree R, Leemans CR (2007) Distress in spouses and patients after treatment for head and neck cancer. The Laryngoscope 117 (2):238-241. doi:10.1097/01.mlg.0000250169.10241.58
12. Tan JY, Molassiotis A, Lloyd-Williams M, Yorke J (2018) Burden, emotional distress and quality of life among informal caregivers of lung cancer patients: An exploratory study. Eur J Cancer Care (Engl) 27 (1). doi:10.1111/ecc.12691
13. Li Q, Lin Y, Xu Y, Zhou H (2018) The impact of depression and anxiety on quality of life in Chinese cancer patient-family caregiver dyads, a cross-sectional study. Health Qual Life Outcomes 16 (1):230. doi:10.1186/s12955-018-1051-3
14. Northouse LL, Katapodi MC, Schafenacker AM, Weiss D (2012) The impact of caregiving on the psychological well-being of family caregivers and cancer patients. Seminars in oncology nursing 28 (4):236-245. doi:10.1016/j.soncn.2012.09.006

15. Hirst M (2005) Carer distress: a prospective, population-based study. Social science & medicine 61 (3):697-708. doi:10.1016/j.socscimed.2005.01.001
16. Custers JA, Tielen R, Prins JB, de Wilt JH, Gielissen MF, van der Graaf WT (2015) Fear of progression in patients with gastrointestinal stromal tumors (GIST): Is extended lifetime related to the Sword of Damocles? Acta oncologica 54 (8):1202-1208. doi:10.3109/0284186X.2014.1003960
17. van de Wal M, Langenberg S, Gielissen M, Thewes B, van Oort I, Prins J (2017) Fear of cancer recurrence: a significant concern among partners of prostate cancer survivors. Psycho-oncology 26 (12):2079-2085. doi:10.1002/pon.4423
18. Perez-Ordonez F, Frias-Osuna A, Romero-Rodriguez Y, Del-Pino-Casado R (2016) Coping strategies and anxiety in caregivers of palliative cancer patients. Eur J Cancer Care (Engl) 25 (4):600-607. doi:10.1111/ecc.12507
19. Kim Y, Wellisch DK, Spillers RL, Crammer C (2007) Psychological distress of female cancer caregivers: effects of type of cancer and caregivers' spirituality. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 15 (12):1367-1374. doi:10.1007/s00520-007-0265-4
20. Selman LE, Brighton LJ, Sinclair S, Karvinen I, Egan R, Speck P, Powell RA, Deskur-Smielecka E, Glajchen M, Adler S, Puchalski C, Hunter J, Gikaara N, Hope J, InSpirit C (2018) Patients' and caregivers' needs, experiences, preferences and research priorities in spiritual care: A focus group study across nine countries. Palliat Med 32 (1):216-230. doi:10.1177/0269216317734954
21. Stroebe M, Schut H, Stroebe W (2007) Health outcomes of bereavement. Lancet 370 (9603):1960-1973. doi:10.1016/S0140-6736(07)61816-9
22. Simon NM (2013) Treating complicated grief. JAMA : the journal of the American Medical Association 310 (4):416-423. doi:10.1001/jama.2013.8614
23. Fujisawa D, Miyashita M, Nakajima S, Ito M, Kato M, Kim Y (2010) Prevalence and determinants of complicated grief in general population. Journal of affective disorders 127 (1-3):352-358. doi:10.1016/j.jad.2010.06.008
24. Kersting A, Brahler E, Glaesmer H, Wagner B (2011) Prevalence of complicated grief in a representative population-based sample. Journal of affective disorders 131 (1-3):339-343. doi:10.1016/j.jad.2010.11.032
25. Newson RS, Boelen PA, Hek K, Hofman A, Tiemeier H (2011) The prevalence and characteristics of complicated grief in older adults. Journal of affective disorders 132 (1-2):231-238. doi:10.1016/j.jad.2011.02.021
26. Guldin MB, Vedsted P, Zachariae R, Olesen F, Jensen AB (2012) Complicated grief and need for professional support in family caregivers of cancer patients in palliative care: a longitudinal cohort study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 20 (8):1679-1685. doi:10.1007/s00520-011-1260-3
27. Allen JY, Haley WE, Small BJ, Schonwetter RS, McMillan SC (2013) Bereavement among hospice caregivers of cancer patients one year following loss: predictors of grief, complicated grief, and symptoms of depression. Journal of palliative medicine 16 (7):745-751. doi:10.1089/jpm.2012.0450
28. Chiu YW, Huang CT, Yin SM, Huang YC, Chien CH, Chuang HY (2010) Determinants of complicated grief in caregivers who cared for terminal cancer patients. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 18 (10):1321-1327. doi:10.1007/s00520-009-0756-6

29. Thomas K, Hudson P, Trauer T, Remedios C, Clarke D (2013) Risk Factors for Developing Prolonged Grief During Bereavement in Family Carers of Cancer Patients in Palliative Care: A Longitudinal Study. J Pain Symptom Manage. doi:10.1016/j.jpainsymman.2013.05.022
30. Pasek M, Debska G, Wojtyna E (2017) Perceived social support and the sense of coherence in patient-caregiver dyad versus acceptance of illness in cancer patients. J Clin Nurs 26 (23-24):4985-4993. doi:10.1111/jocn.13997
31. Dumont I, Dumont S, Mongeau S (2008) End-of-life care and the grieving process: family caregivers who have experienced the loss of a terminal-phase cancer patient. Qual Health Res 18 (8):1049-1061. doi:10.1177/1049732308320110
32. Nijboer C, Tempelaar R, Triemstra M, van den Bos GA, Sanderman R (2001) The role of social and psychologic resources in caregiving of cancer patients. Cancer 91 (5):1029-1039
33. Traa MJ, De Vries J, Roukema JA, Den Oudsten BL (2016) The association between patient's and partner's fatigue in couples coping with colorectal cancer: a longitudinal study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 24 (10):4113-4121. doi:10.1007/s00520-016-3226-y
34. Peters ME, Goedendorp MM, Verhagen SA, Smilde TJ, Bleijenberg G, van der Graaf WT (2014) A prospective analysis on fatigue and experienced burden in informal caregivers of cancer patients during cancer treatment in the palliative phase. Acta oncologica:1-7. doi:10.3109/0284186X.2014.953254
35. Kim Y, Carver CS, Spillers RL, Love-Ghaffari M, Kaw CK (2012) Dyadic effects of fear of recurrence on the quality of life of cancer survivors and their caregivers. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 21 (3):517-525. doi:10.1007/s11136-011-9953-0
36. Mellon S, Kershaw TS, Northouse LL, Freeman-Gibb L (2007) A family-based model to predict fear of recurrence for cancer survivors and their caregivers. Psycho-oncology 16 (3):214-223. doi:10.1002/pon.1074
37. Matthews BA (2003) Role and gender differences in cancer-related distress: a comparison of survivor and caregiver self-reports. Oncology nursing forum 30 (3):493-499. doi:10.1188/03.ONF.493-499
38. Mellon S, Northouse LL (2001) Family survivorship and quality of life following a cancer diagnosis. Res Nurs Health 24 (6):446-459. doi:10.1002/nur.10004
39. Cohee AA, Adams RN, Johns SA, Von Ah D, Zoppi K, Fife B, Monahan PO, Stump T, Cella D, Champion VL (2017) Long-term fear of recurrence in young breast cancer survivors and partners. Psycho-oncology 26 (1):22-28. doi:10.1002/pon.4008
40. Jadalla A, Ginex P, Coleman M, Vrabel M, Bevans M (2020) Family Caregiver Strain and Burden: A Systematic Review of Evidence-Based Interventions When Caring for Patients With Cancer. Clin J Oncol Nurs 24 (1):31-50. doi:10.1188/20.CJON.31-50
41. Treanor CJ, Santin O, Prue G, Coleman H, Cardwell CR, O'Halloran P, Donnelly M (2019) Psychosocial interventions for informal caregivers of people living with cancer. Cochrane Database Syst Rev 6:CD009912. doi:10.1002/14651858.CD009912.pub2
42. Pendergrass A, Mittelman M, Graessel E, Ozbe D, Karg N (2019) Predictors of the personal benefits and positive aspects of informal caregiving. Aging Ment Health 23 (11):1533-1538. doi:10.1080/13607863.2018.1501662
43. Sannes TS, Yeh IM, Gray TF (2020) Caring for loved ones with cancer during the COVID-19 pandemic: A double hit risk for social isolation and need for action. Psycho-oncology. doi:10.1002/pon.5466

44. Zarit SH, Reever KE, Bach-Peterson J (1980) Relatives of the impaired elderly: correlates of feelings of burden. The Gerontologist 20 (6):649-655. doi:10.1093/geront/20.6.649
45. Given CW, Given B, Stommel M, Collins C, King S, Franklin S (1992) The caregiver reaction assessment (CRA) for caregivers to persons with chronic physical and mental impairments. Res Nurs Health 15 (4):271-283. doi:10.1002/nur.4770150406
46. Pot AM, van Dyck R, Deeg DJ (1995) [Perceived stress caused by informal caregiving. Construction of a scale]. Tijdschrift voor gerontologie en geriatrie 26 (5):214-219
47. Rohleder N, Marin TJ, Ma R, Miller GE (2009) Biologic cost of caring for a cancer patient: dysregulation of pro- and anti-inflammatory signaling pathways. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27 (18):2909-2915. doi:10.1200/JCO.2008.18.7435
48. Lee S, Colditz GA, Berkman LF, Kawachi I (2003) Caregiving and risk of coronary heart disease in U.S. women: a prospective study. Am J Prev Med 24 (2):113-119. doi:10.1016/s0749-3797(02)00582-2
49. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K, Committee EG (2017) Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 28 (suppl_4):iv119-iv142. doi:10.1093/annonc/mdx225



Appendix

Appendix

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Inleiding

In 2018 werd in Nederland bij 116.537 inwoners de diagnose kanker gesteld en overleden 45.206 mensen aan de gevolgen van kanker. Voor kanker kunnen de volgende behandelingen worden gegeven: operatie, bestraling en/of systemische behandeling. Systemische behandeling wordt ingedeeld in chemotherapie, doelgerichte therapie, immunotherapie en/of hormonale therapie. Systemische behandeling wordt bij een curatieve, op genezing gerichte, behandeling in drie verschillende fasen gegeven , te weten 1) neo-adjuvant (voorafgaan aan operatie of bestraling), 2) concomitant (tegelijk met radiotherapie) en 3) adjuvant (na operatie of bestraling). Wanneer een curatieve behandeling niet meer mogelijk is, wordt er vaak een systeembehandeling met palliatieve intentie gegeven. Het doel hiervan is levensverlenging met behoud of verbetering van de kwaliteit van leven. Tijdens deze verschillende fases in de behandeling voor kanker komt een patiënt voor vele uitdagingen te staan en de steun van (een) mantelzorger(s) is daarbij onmisbaar.

Mantelzorgers en hun uitdagingen

Er zijn in Nederland 4,4 miljoen mantelzorgers (25%) die zorg verlenen aan een naaste. Hiervan verlenen 750.000 mantelzorgers langdurige zorg (> 3 maanden) en/of voor meer dan 8 uur per dag. Het is niet precies bekend hoeveel van deze mantelzorgers zorgen voor een patiënt met kanker. Mantelzorg kan worden verleend door een partner, ouders, kind, broer of zus, maar ook door een goede vriend of buur. De zorg van mantelzorgers bestaat uit praktische en emotionele ondersteuning. Als gevolg van deze zorg kan een mantelzorger problemen ervaren, zoals overbelasting en distress, wat ook consequenties kan hebben op voor de eigen kwaliteit van leven en fysieke gezondheid. Daarnaast kunnen mantelzorgers, net als de patiënt, angst voor de terugkeer van kanker bij de patiënt ervaren.

(Over)belasting

Overbelasting ontstaat wanneer de gevolgen van de zorg voor de patiënt met kanker niet meer in balans zijn met de veerkracht van de mantelzorger en zijn of haar mogelijkheden om met de nieuwe situatie om te gaan. Risicofactoren voor overbelasting zijn divers en bestaan uit demografische factoren (vrouw, samenleven met de patiënt), psychologische factoren (depressie, beperkte coping- strategieën, stress), sociale factoren (leven in sociaal isolement), financiële factoren (onderbreking van werk, financiële zorgen) en zorg-

gerelateerde factoren (groter aantal uren besteed aan mantelzorgen). In Nederland zijn 380.000 mantelzorgers overbelast. Welk aandeel hiervan mantelzorger van patiënten met kanker zijn is niet bekend. Het geeft wel aan dat er een kwetsbare groep mantelzorgers is die extra ondersteuning zou kunnen gebruiken.

Distress, depressie en gecompliceerde rouw

De definitie van distress is "emotionele, sociale, spirituele of fysieke pijn of lijden dat kan leiden tot verdriet, somberheid, angst of eenzaamheid". Distress komt vaak samen voor met overbelasting. De gevolgen van distress bij de mantelzorger kunnen zijn dat 1) patiënten op langere termijn moeite krijgen om zich aan te passen aan hun ziekte en situatie, 2) patiënten meer angst ervaren door de angst van de mantelzorger, 3) mantelzorgers niet in staat zijn om te zorgen voor de patiënt en 4) zij gevolgen ervaren op hun fysieke gezondheid, zoals het ontwikkelen van hart- en vaatziekten. De oorzaken waardoor een mantelzorger meer distress ervaart verschillen per fase waarin de patiënt zich bevindt. Over het algemeen kan een mantelzorger distress ervaren door 1) de behandeling van de patiënt (twijfel over de effectiviteit van de behandeling, distress bij de patiënt door bijwerkingen en hoe hiermee om te gaan, onvoorbereid complexe zorg moeten leveren), 2) psychosociale factoren (sociale isolatie, veranderingen in rol in sociale leven, overspoeld voelen, de patiënt helpen emoties te verwerken, complexe verhoudingen binnen gezin/ familie), en / of 3) onvervulde behoeften (psychosociaal, medisch, financieel, kennis). Ongeveer 20% van de mantelzorgers van patiënten met kanker ervaart distress en er zijn aanwijzingen dat vrouwelijke mantelzorgers vaker distress ervaren dan mannelijke mantelzorgers.

Distress kan op langere termijn leiden tot depressie. Depressie wordt gekenmerkt door gevoelens van somberheid, wanhoop, verlies van energie, gebrek aan een gevoel van eigenwaarde en hierdoor moeite hebben met het omgaan met normale dagelijkse bezigheden. Het percentage mantelzorgers van patiënten met kanker dat depressieve kenmerken heeft ligt tussen de 12 en 41% en hangt samen met de fase waarin de patiënt behandeld wordt.

Nauw verbonden met distress en depressie is gecompliceerde rouw. Rouw is een normale respons op een groot verlies in het leven. Normaal gesproken neemt de intensiteit van deze rouw in de loop van de tijd af zonder dat daarvoor extra hulp nodig is. Bij gecompliceerde rouw wijkt de rouw af van normale rouw (in culturele en maatschappelijke context gezien) door de duur, intensiteit of een combinatie van beiden. Gecompliceerde rouw kenmerkt zich door een meer chronische, intensere reactie op het verlies van een naaste of juist door

het ontbreken van een reactie op het verlies of door een verlate reactie op het verlies. Een natuurlijk herstel treedt niet of nauwelijks op. Het is belangrijk om te weten dat symptomen van gecompliceerde rouw overeenkomsten vertonen met symptomen van distress en depressie. Gecompliceerde rouw kan ook samen met depressie voorkomen of kan verergering van depressieve symptomen geven.

Gezondheids-gerelateerde kwaliteit van leven en vermoeidheid

Gezondheids-gerelateerde kwaliteit van leven wordt gedefinieerd als de mate waarin de gezondheid van een persoon impact heeft op zijn of haar mogelijkheid om te functioneren en hoe zijn of haar gezondheid het fysieke, mentale en sociale welzijn beïnvloedt. Er zijn studies die laten zien dat stress bij mantelzorgers een negatief effect kan hebben op hormonale- en ontstekingsprocessen. Ook lijkt er een verband te bestaan tussen mantelzorgen en een verhoogd risico op hart- en vaatziekten. Dit zal de gezondheids-gerelateerde kwaliteit van leven van mantelzorgers kunnen beïnvloeden.

Onder mantelzorgers lijkt ook ernstige vermoeidheid een probleem te zijn. Bij mantelzorgers van patiënten in de palliatieve fase bleek dat 23% van deze mantelzorgers matig tot ernstig vermoeidheid zijn. Hier is echter nog weinig onderzoek naar gedaan.

Angst voor terugkeer van kanker

Onder patiënten met kanker is angst voor terugkeer van de ziekte (angst voor recidief) een belangrijk probleem. Van de patiënten die succesvol behandeld zijn voor kanker heeft ongeveer 49% last van angst voor recidief en dit percentage neemt niet af in de loop van de tijd. Ernstige angst voor terugkeer van kanker is geassocieerd met minder goede zelfzorg, distress en een hogere zorgconsumptie. Er is verder nog weinig bekend over angst voor recidief bij mantelzorgers. Er is wel een studie verricht bij partners van patiënten met prostaatkanker. Van hen had 51% angst voor ziekteprogressie (toename van ziekte).

DEEL I: MANTELZORGERS VAN PATIËNTEN TIJDENS BEHANDELING

Mantelzorgers van patiënten die (in opzet) curatief behandeld worden

Wanneer iemand behandeld wordt voor kanker is het essentieel dat deze behandeling zo optimaal mogelijk en in zijn geheel gegeven kan worden. Mantelzorgers zijn daarbij onmisbaar en kunnen door deze zorg belast raken.

Hoofd-halskanker

In Nederland werd in 2019 bij 2839 patiënten de diagnose hoofd-halskanker gesteld, waarvan bij ongeveer de helft van hen het (ziekte) stadium III of IV betrof. Risicofactoren voor het krijgen van hoofd-halskanker zijn roken en overmatig alcoholgebruik. Daarnaast zijn er patiënten die hoofd-halskanker krijgen als gevolg van het humaan papilloma virus (HPV). Patiënten met lokaal uitgebreid hoofd-halskanker (stadium III/IV) worden curatief behandeld. Hiervoor ondergaan zij concomitant chemo- en radiotherapie gedurende 6 of 7 weken. Bijwerkingen die vaak voorkomen als gevolg van deze behandeling zijn onder andere vermoeidheid, slijmvliesschade en ontsteking van de huid. De behandeling en de gevolgen hiervan kunnen leiden tot distress en het is bekend dat het percentage depressies onder patiënten met hoofd-halskanker hoger ligt (40%) dan bij patiënten met andere soorten kanker (12.5%) en de algemene bevolking (3%). Ondersteuning tijdens de behandeling door hun mantelzorger(s) is onmisbaar. Dit kan de mantelzorger echter ook belasten.

In **hoofdstuk 2** wordt een studie beschreven over mantelzorgers van patiënten die behandeld werden met concomitant chemo- en radiotherapie in verband met lokaal uitgebreid hoofd-halskanker. Allereerst is het verloop van de belasting en vermoeidheid van de mantelzorger in relatie tot de distress en vermoeidheid van de patiënt onderzocht. Daarnaast is gekeken naar risicofactoren voor overbelasting en vermoeidheid bij de mantelzorger nadat de patiënt de behandeling heeft afgerond.

We vonden dat de vermoeidheid en belasting van mantelzorgers gemiddeld genomen het hoogste was op het moment dat de vermoeidheid en distress van patiënt ook het hoogste was, namelijk op één week na het einde van de chemoradiotherapie. Op dat moment werd bij de patiënt ook de laagste gezondheids-gerelateerde kwaliteit van leven gemeten. De gemiddelde mate van belasting en vermoeidheid van de mantelzorgers daalde weer naar het niveau van voor de start van de behandeling. Overbelaste en vermoeide vrouwelijke partners

die zorgden voor een patiënt met een grote daling in zijn of haar gezondheids-gerelateerde kwaliteit van leven hadden een groter risico op overbelasting na het einde van de behandeling van de patiënt. Vermoeidheid bij de mantelzorger bij aanvang van de behandeling bleek een risicofactor te zijn voor vermoeidheid na het einde van de behandeling.

Op grond van deze resultaten lijkt het essentieel om voor het starten van de behandeling van de patiënt met lokaal vergevorderd hoofd-halskanker mantelzorgers te identificeren die bij aanvang al problemen ervaren om juist hen extra te kunnen ondersteunen en problemen op langere termijn te voorkomen.

Darmkanker

In 2019 werd in Nederland bij 9237 patiënten de diagnose darmkanker gesteld, waarvan bij ongeveer 65% stadium II of III ziekte betrof. Na resectie van de tumor zal bij een deel van deze patiënten adjuvante chemotherapie geadviseerd worden om de kans op genezing te vergroten. De meest voorkomende bijwerkingen van deze chemotherapie zijn het handvoetsyndroom, misselijkheid, braken maar vooral ook zenuwschade aan de handen en voeten. Dit laatste is niet altijd (of veelal) niet omkeerbaar. Er is weinig bekend over mantelzorgers van patiënten die een dergelijke, in opzet curatieve, behandeling ondergaan voor darmkanker.

In Nederland is wel eerder gekeken naar de ervaring(en) van naasten van darmkankerpatiënten die een operatie hadden ondergaan en die nadien tenminste een prognose van 6 maanden hadden. Jonge en vrouwelijke mantelzorgers bleken meer behoefte te hebben aan ondersteuning bij hun taken als mantelzorger. Ook werd er een relatie gevonden tussen een negatieve ervaring als mantelzorger en 1) een lager inkomen, 2) zorgen voor een meer afhankelijke patiënt, 3) spanning binnen de relatie en 4) meer zorgtaken hebben. Verder werd beschreven dat deze groep jonge en vrouwelijke mantelzorgers meer risico had op het ontwikkelen van een depressie op langere termijn. Ook mantelzorgers die een lagere sociale betrokkenheid ervaarden hadden ditzelfde risico op depressies.

In **hoofdstuk 3** wordt een studie beschreven bij mantelzorgers van patiënten die in opzet curatief behandeld werden voor darmkanker. Er werd specifiek gekeken naar 1) het verloop van de belasting en distress van mantelzorgers voor, tijdens en na de behandeling van de patiënt en is er gekeken naar hoeveel mantelzorgers een hoge mate van belasting en distress ondervonden, 2) mogelijke risicofactoren voor een hoge ervaren belasting en distress tijdens en maanden na het einde van de behandeling, 3) de associatie tussen de belasting en distress van mantelzorgers en de distress van de patiënt en 4) het beloop van de gezondheids-gerelateerde kwaliteit van leven van de mantelzorgers en de associatie tussen hun belasting en distress en die van de patiënt.

Gemiddeld genomen was de ervaren belasting en distress van mantelzorgers tijdens en na de behandeling laag en als het wel verhoogd was nam het ook weer af in de loop van de tijd. Er was echter een groep van mantelzorgers die voor het starten van de chemotherapie een hoge mate van belasting (12%; n=7/58) en distress (27%; n=16/60) ervaarde (12%; n=7/58). Bij respectievelijk 8% (n=4/50) en 19% (n=9/48) van de mantelzorgers werd 3 maanden na het einde van de behandeling nog een hoge mate van belasting en distress gezien. Belasting voor en tijdens de behandeling van de patiënt vormt een risicofactor voor de mate van ervaren belasting maanden na het einde van de behandeling van de patiënt. Ditzelfde werd gevonden voor distress.

Deze studie liet zien dat er een kwetsbare groep mantelzorgers is en waar het van toegevoegde waarde kan zijn om al voor het starten van de behandeling ondersteuning te bieden.

Mantelzorgers van patiënten tijdens langdurige behandeling

Mantelzorgers van patiënten die langdurig worden behandeld voor gastro-intestinale stromatumor (GIST)

Een GIST is een zeldzame kwaadaardige wekedelen tumor, die meestal uitgaat van de maag- of darmwand en uit kan zaaien in de buik of naar de lever. In Nederland werd in 2018 bij ongeveer 400 patiënten een GIST vastgesteld. Deze vorm van kanker staat erom bekend dat deze ongevoelig is voor bestraling en chemotherapie, waardoor lange tijd de levensverwachting van de patiënten met een GIST beperkt was. In 2000 heeft het medicijn imatinib, een doelgericht geneesmiddel, ervoor gezorgd dat de levensverwachting van patiënten met GIST aanzienlijk verbeterde van gemiddeld minder dan een jaar naar gemiddeld meer dan 5 jaar. Daarmee werd dit medicijn de hoeksteen van de behandeling bij gemetastaseerde ziekte. Later bleek imatinib ook effectief als adjuvante behandeling van GIST, waarbij de behandelduur 3 jaar is. Inmiddels zijn er meerdere doelgerichte behandelingen voor GIST beschikbaar. Ondanks deze indrukwekkende vooruitgang in de overleving krijgen patiënten ook te maken met uitdagingen. De ervaren bijwerkingen van de jarenlange dagelijkse medicijnen zijn vermoeidheid, diarree, misselijkheid en braken, vochtophoping rondom de ogen, spierkrampen en huiduitslag. Daarnaast hebben veel patiënten te maken met angst voor recidief of progressie van de ziekte. Dit kan ook impact hebben op het welzijn van hun naasten, zoals zorgverleners geobserveerd hebben.

In **hoofdstuk 4** wordt een studie beschreven waarin is gekeken naar 1) de mate van belasting en distress van mantelzorgers van patiënten die langdurig behandeld worden voor GIST, 2) hun gezondheids-gerelateerde kwaliteit van leven, tevredenheid over hun relatie en sociale ondersteuning en 3) mantelzorgers die een hoge mate van belasting en distress ervaarden vergeleken worden met mantelzorgers die een lage mate van belasting en distress ervaarden.

Er werd gevonden dat de mate van ervaren belasting en distress bij de mantelzorgers (n=61) in deze studie gemiddeld laag was. De ervaren gezondheids-gerelateerde kwaliteit van leven van deze mantelzorgers was vergelijkbaar met die beschreven is in de algemene bevolking. Hun mate van tevredenheid over hun relatie was hoog en ze ervaarden weinig tekortkomingen in de steun vanuit hun sociale netwerk. De helft van de patiënten ondervond hinderlijke of ernstige bijwerkingen van de behandeling en 34% ervaarde distress. Kijkend naar de mantelzorgers ervaarde 10% van hen een hoge mate van belasting en 23% een hoge mate van distress. Er is een relatie te bestaan tussen de mate van distress van de patiënt en de mate van belasting en distress van de mantelzorger. Mantelzorgers met een hoge mate van ervaren belasting gaven vaker aan een lagere mate van mentale gezondheid te ervaren, minder vitaal te zijn en meer distress te ervaren. Een hogere mate van belasting werd ook vaker gerapporteerd door 1) de niet-partner mantelzorgers, 2) mantelzorgers van patiënten die meer bijwerkingen ondervonden, 3) mantelzorgers die meer uren besteedden aan zorgen voor de patiënt en 4) mantelzorgers die voor meer dan één persoon zorgden. Mantelzorgers die meer distress ervaarden gaven vaker aan 1) een lagere mate van algehele gezondheids-gerelateerde kwaliteit van leven te ervaren, 2) meer belasting te ervaren, 3) sociaal minder te functioneren, 4) moeite te hebben met het omgaan met fysieke en emotionele problemen, 5) een lagere mate van mentale gezondheid te ervaren en 6) minder vitaal te zijn. Daarnaast werd ook gezien dat mantelzorgers met meer ervaren distress zorgden voor 1) meer afhankelijke patiënten en 2) meer dan één persoon tegelijk.

Deze studie laat zien dat het belangrijk is dat er aandacht is voor het welzijn van een kleine, maar kwetsbare groep mantelzorgers waarvan de naasten langdurig behandeld moeten worden voor kanker en dat de bewustwording hiervan een belangrijke eerste stap kan zijn.

DEEL II:
MANTELZORGERS VAN PATIËNTEN DIE KANKER OVERLEEFD HEBBEN

Mantelzorgers van patiënten die succesvol behandeld zijn voor prostaatkanker
Angst voor de recidief komt voor bij bijna de helft (49%) van de patiënten die eerder in opzet curatief zijn behandeld voor prostaatkanker. Deze angst neemt niet af in de loop van de tijd. Het is bekend dat angst voor terugkeer van kanker gepaard kan gaan met ongezond gedrag, distress en toegenomen zorgconsumptie. Het is denkbaar dat ook de mantelzorgers van deze patiënten deze angst ervaren, echter hierover is weinig bekend.

In **hoofdstuk 5** wordt een studie beschreven over partners van patiënten die eerder een in opzet curatieve behandeling van prostaatkanker ondergingen (n=168). Er werd gekeken naar 1) hoeveel partners angst hebben voor recidief van prostaatkanker, 2) de relatie tussen de angst voor terugkeer van de ziekte tussen de partner en de patiënt, 3) de demografische gegevens van partner en patiënten die een hoge mate van angst voor recidief ervaren en 4) de relatie tussen een hoge mate van angst voor recidief bij de partners en hun gezondheids-gerelateerde kwaliteit van leven.

Er werd gevonden dat ongeveer evenveel partners (35%) en patiënten (38%) ernstige angst voor de terugkeer van de ziekte ervaarden. Een hogere mate van angst voor terugkeer van de ziekte bij de partner was geassocieerd met meer angst bij de patiënt, hetgeen ook het geval was als de partner jonger was. Vergeleken met partners met een lage angst voor recidief scoorden partners met een hoge angst voor recidief significant lager op sociaal functioneren, mentale gezondheid en vitaliteit. Zij ervaarden ook significant vaker moeite met vervullen van dagelijkse taken door moeilijkheden in hun emotioneel functioneren.

Deze studie benadrukt dat ernstige angst voor recidief ook een probleem kan zijn bij de partners van patiënten in opzet curatief behandeld zijn voor prostaatkanker. Het wordt aanbevolen om bij het vormgeven van toekomstige studies en beleid rondom angst voor recidief ook de partner te betrekken.

DEEL III: MANTELZORGERS VAN OVERLEDEN PATIËNTEN

Nabestaanden van patiënten die deel hebben genomen aan experimentele therapie in de laatste levensfase

Wanneer een patiënt deelneemt in een fase-I experimentele studie is er geen reguliere behandeling voor de kanker meer voorhanden en is de prognose beperkt. Een patiënt die wil deelnemen aan een fase-I studie moet nog in een goede conditie verkeren. Er is een hele kleine kans dat de behandeling effect heeft op de kanker, en er kunnen wel belangrijke bijwerkingen optreden. Dit maakt de positie van de patiënt kwetsbaar in zijn of haar laatste levensfase. De meeste studies naar deze kwetsbaarheid hebben het perspectief van de patiënt en de zorgverleners belicht. Het perspectief van de mantelzorgers van de patiënt is nooit onderzocht.

In **hoofdstuk 6** wordt een studie beschreven met partners van patiënten die overleden zijn na deelname aan een experimentele behandeling in de laatste levensfase. Er is gekeken naar 1) hoe de partner van de patiënt terugkijkt op de deelname van de patiënt aan een fase-I studie en 2) naar eventuele problemen die de partner nog kan ervaren zoals distress, depressie, gecompliceerde rouw en hun gezondheids-gerelateerde kwaliteit van leven.

Wat werd gevonden is dat, 2 jaar na het overlijden van de patiënt, partners aangaven dat de deelname van de patiënt aan een fase-I studie een negatief effect had op de gezondheids-gerelateerde kwaliteit van leven van de patiënt. Daar tegenover stond dat slechts 5% (n=3/58) van de partners uiteindelijk spijt had van deze deelname. Vergeleken met de gezonde populatie, scoorden de partners gemiddeld genomen lager op sociaal en mentaal functioneren. Verder had 19% (n=11/58) van de nabestaanden symptomen van een depressie, 36% (n=21/58) ervaarde distress en 46% (n=26/57) had symptomen van gecompliceerde rouw.

Deze studie onderstreept dat verder onderzoek nodig is naar de oorzaak van deze problemen na het overlijden van de patiënt en welke relatie dit heeft met de behandeling met experimentele therapie in de laatste levensfase.

TOT SLOT

In **hoofdstuk 8** wordt de inhoud van alle hoofdstukken in relatie tot elkaar bediscussieerd, welke implicaties de bevindingen kunnen hebben voor de dagelijkste praktijk en worden aanbevelingen gedaan voor toekomstig onderzoek. De studies in dit proefschrift bevestigen hetgeen we in de praktijk zien, namelijk dat er een groep mantelzorgers is die kwetsbaar is en dat problemen bij het starten van de behandeling een risicofactor kunnen zijn voor het hebben van problemen op de langere termijn. In elke studie was een kwetsbare groep mantelzorgers te identificeren en vooral de mantelzorgers van patiënten die behandeld worden voor hoofd-halskanker en de mantelzorgers van patiënten die deelnemen aan experimentele behandeling in de laatste fase van hun leven vielen op door de mate van problemen die zij ervaarden.

Essentieel is om een onderscheid te kunnen maken tussen een normale reactie op een stressvolle situatie in het leven van de mantelzorger en wanneer dit overgaat in een probleem die het dagelijks leven van de mantelzorger dusdanig beïnvloedt dat het eigen functioneren beperkt wordt. Twee studies in dit proefschrift laten zien dat problemen voor het starten van de behandeling, zoals belasting, distress en vermoeidheid, aandacht behoeven vroeg tijdens de behandeling van de patiënt, omdat dit op langere termijn een risicofactor blijkt voor blijvende problemen. Belangrijk bij verdere ondersteuning van mantelzorgers is het samenspel tussen het herkennen van problemen van de mantelzorger door zorgprofessionals, het erkennen van de mantelzorger dat er een probleem is en de mogelijkheden om deze problemen te objectiveren en op te lossen. Net als de zorg van de patiënt die steeds verder gepersonaliseerd wordt, zal ook de zorg voor mantelzorgers maatwerk zijn. Samenwerking tussen zorgverleners in de eerste, tweede en derde lijn is daarvoor onmisbaar. De huisarts zal een centrale rol spelen, aangezien de huisarts als enige een behandelrelatie met de mantelzorger heeft. Daarnaast zal ook zijn rol als "familie dokter" van toegevoegde waarde zijn aangezien de huisarts het systeem van de patiënt en de mantelzorger goed kent, wat helpt om zorg op maat te leveren.

Er is steeds meer kennis over hoe mantelzorgers ondersteund kunnen worden. Het is bekend dat psycho-educatie, ondersteunende interventies, mindfulness-based stress-reductie en cognitieve gedragstherapie de ervaren belasting van mantelzorgers kunnen verlichten, waar ook behoefte is aan meer kennis over copingsmechanismen van mantelzorgers en wat nader onderzocht dient te worden.

Verder zal de belasting en distress van de mantelzorger ook gevolgen kunnen hebben voor de fysieke gezondheid van de mantelzorger. Het onderzoek hiernaar is nog beperkt en kennis hierover kan een meer compleet beeld geven welke

consequenties mantelzorgen kan hebben. Daarnaast kan deze kennis, samen met de verder te verwerven kennis over de mentale gevolgen van het mantelzorgen, leiden tot proactieve en preventieve interventies om problemen op langere termijn te voorkomen.

Kijkend naar nieuwe ontwikkelingen, van nieuwe behandelingen als immunotherapie tot de gevolgen die de coronapandemie heeft op het welzijn van mantelzorgers, is het belangrijk om door middel van verder onderzoek te kijken hoe welzijn van mantelzorgers zich hiertoe verhoudt.

Appendix

PhD portfolio

PHD PORTFOLIO

Institute for Health Sciences
Radboudumc

Name PhD candidate: S.M.C.H. Langenberg	**PhD period:** 01-02-2013 – 31-12-2020
	Promotor(s):
Department: Medical Oncology	Prof. dr. W.T.A. van der Graaf prof. dr. J.B. Prins prof. dr. C.M.L. van Herpen
Graduate School: Radboud Institute for Health Sciences	**Co-promotor(s):** dr. A.N.M. Wymenga

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- *NCEPB (RIHS) introduction course*	2013	2.0
- *BROK course*	2013	2.0
- *NvVO introduction course for clinical and fundamental oncology*	2013	1.5
- *Workshop "how to handle your data"*	2013	0.2
- *Academic writing*	2013	3.0
- *Course "presenting for PhD candidates" (ABN Amro Spies & spreken)*	2013	0.2
- *Course "balans werk-privé" (PAO Heyendael)*	2014	0.5
- *BROK refresher course*	2017	0.5
- *8-daagse training palliatieve zorg voor medisch specialisten*	2018-2019	3
b) Seminars & lectures		
- *'De onderzoeker aan zet Innovatief onderzoek en kwaliteitsborging. Kan dat samen?*	2013	0.2
- *Jonge oncologen avond (oral)*	2014	0.5
- *Jonge oncologen avond*	2015	0.2
c) Symposia & congress		
- *ECCO congress Amsterdam (poster)*	2013	1.0
- *ESMO congress Madrid (2 posters)*	2014	1.75
- *NVPO congress Utrecht (oral)*	2014	0.5
- *Nederlandse Sarcomen Studiedag, AvL-NKI, Amsterdam (oral)*	2014	0.5
- *Symposium Junior onderzoekers proactieve palliatieve zorg (oral)*	2014	0.5
- *Oncologie symposium Medisch Spectrum Twente (oral)*	2014	0.5
- *NVPO congress Utrecht (2 posters)*	2015	0.5
- *Palliatieve zorg: Intuïtie, wijsheid of wetenschap (oral)*	2019	0.75
- *NVMO oncologie dagen*	2019	0.5
- *NVMO post-ASCO*	2019	0.25
- *NVMO oncologie dagen*	2020	0.5
- *NVMO post-ASCO*	2020	0.25

	Year(s)	ECTS
TRAINING ACTIVITIES		
d) Other		
- *Journal club Psychosocial Oncology*	2013-2015	3
- *Gammaraad Psychosocial Oncology*	2013-2015	1
- *Member of the RIHS PhD council*	2013-2015	1
- *PhD Council organizing workshops & visit to Ministry of Health, Well-being and sports*	2013-2015	4.0
- *Co-organizing RIHS PhD retreat*	2014	3.0
TEACHING ACTIVITIES		
e) Lecturing		
- *Tutor Cancer Research, bachelor BMW Radboudumc*	2013	2
- *Oncology course Radboud Honours progam bachelor student (Medicine and BMW)*	2014	0.5
- *Bachelor geneeskunde - palliative care Radboudumc*	2018-now	3
f) Supervision of internships / other	NA	
TOTAL		38.8

Radboud Universiteit Radboudumc

Appendix

Research data management

RESEARCH DATA MANAGEMENT

The results of the studies in this thesis are based on human studies. All procedures performed were in accordance 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For all studies in this thesis, approval of the medical ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen was granted (2009/191; 2010/461; 2013/184; 2013/278; 2013/393). Informed consent was obtained from all participants.

All the document of this study, including data of patients and their informal caregivers, are deposited on the Radboudumc Medical Oncology server (\\Umcfs074\oncodata$\Mantelzorgstudie). This folder is created for this project and only accessible for authorized personnel. For all the studies in this thesis we used paper and pencil questionnaires. The questionnaires and informed consent forms are stored in the archives of the department of Medical Oncology and Medical Psychology. Data management and monitoring were performed by using Microsoft office Excel files and "Statistical Package for the Social Sciences" (SPSS). All these files were stored on the Radboudumc Medical Oncology server (\\Umcfs074\oncodata$\Mantelzorgstudie). The questionnaires were coded, providing each participant an unique code. The databases used for analyses of the studies in this thesis only contained coded anonymous information and hereby warranted the privacy of the participants. The data stored in the archives will be saved for 15 years after termination of the studies. The datasets analyzed for the studies in this thesis are available from the project leader on reasonable request.

Appendix

List of publications

LIST OF PUBLICATIONS

1. Schellekens RC, Olsder GG, **Langenberg SM**, Boer T, Woerdenbag HJ, Frijlink HW, Kosterink JG, Stellaard F (2009) Proof-of-concept study on the suitability of 13C-urea as a marker substance for assessment of in vivo behaviour of oral colon-targeted dosage forms. Br J Pharmacol 158 (2):532-540. doi:10.1111/j.1476-5381.2009.00302.x
2. **Langenberg SM**, Peters ME, van der Graaf WT, Wymenga AN, Prins JB, van Herpen CM (2016) How did partners experience cancer patients' participation in a phase I study? An observational study after a patient's death. Palliative & supportive care 14 (3):241-249. doi:10.1017/S1478951515000887
3. Westdorp H, **Langenberg SM**, Kramers C, Verhagen CA (2017) Gebruik van comedicatie tijdens palliatieve sedatie. Saneren of continueren? Nederlands tijdschrift voor geneeskunde 161:D773
4. van de Wal M, **Langenberg S**, Gielissen M, Thewes B, van Oort I, Prins J (2017) Fear of cancer recurrence: a significant concern among partners of prostate cancer survivors. Psycho-oncology 26 (12):2079-2085. doi:10.1002/pon.4423
5. **Langenberg S**, Reyners AKL, Wymenga ANM, Sieling GCM, Veldhoven CMM, van Herpen CML, Prins JB, van der Graaf WTA (2019) Caregivers of patients receiving long-term treatment with a tyrosine kinase inhibitor (TKI) for gastrointestinal stromal tumour (GIST): a cross-sectional assessment of their distress and burden. Acta oncologica 58 (2):191-199. doi:10.1080/0284186X.2018.1518592
6. **Langenberg S**, van Herpen CML, van Opstal CCM, Wymenga ANM, van der Graaf WTA, Prins JB (2019) Caregivers' burden and fatigue during and after patients' treatment with concomitant chemoradiotherapy for locally advanced head and neck cancer: a prospective, observational pilot study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 27 (11):4145-4154. doi:10.1007/s00520-019-04700-9
7. **Langenberg S**, Poort H, Wymenga ANM, de Groot JW, Muller EW, van der Graaf WTA, Prins JB, van Herpen CML (2020) Informal caregiver well-being during and after patients' treatment with adjuvant chemotherapy for colon cancer: a prospective, exploratory study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. doi:10.1007/s00520-020-05738-w

Appendix

Dankwoord

DANKWOORD

Mijn proefschrift afronden heb ik niet kunnen doen zonder heel veel steun en hulp van de mensen om mij heen. Ik heb er dan ook erg naar uit gekeken om dit dankwoord te mogen schrijven. Allereerst om het moment waarop je dat mag doen, namelijk wanneer het einde echt in zicht is. Bovenal omdat ik zoveel dankbaarheid voel voor iedereen die op mijn pad is gekomen sinds de start van mijn promotietraject. Dit is toch het uitgelezen moment om daar eens goed bij stil te staan. Nou ben ik nooit iemand van weinig woorden geweest, dus zet je schrap, daar gaan we!

Allereerst wil ik alle **mantelzorgers** en **patiënten** die deel hebben willen nemen aan mijn onderzoek bedanken. Het heeft mij elke keer verwonderd dat mensen op zo'n moeilijk en stressvol moment in hun leven bereid zijn om deel te nemen aan onderzoek. Het altruïsme, wat vaak de basis was voor hun deelname aan mijn studies, vind ik bewonderenswaardig. Het was voor mij een extra motivatie om dit proefschrift naar mijn beste kunnen af te ronden.

Professor Van der Graaf, beste Winette, hartelijk dank dat ik dit promotietraject onder jouw supervisie heb mogen doen. Jouw kritische blik en deskundigheid op vele gebieden zijn van grote waarde geweest voor mijn onderzoek. Je hebt voor mij ook veel kansen gecreëerd om mijn onderzoek te presenteren en mij gestimuleerd om dat te doen. Daarnaast heb je rondom life-changing events, zoals bij de geboorte van mijn twee kinderen, altijd jouw betrokkenheid getoond. Dat heb ik echt gewaardeerd. Dankjewel.

Professor Prins, beste Judith, je hebt mij alle ruimte gegeven om te kunnen groeien als onderzoeker. Jouw kennis en deskundigheid op het gebied van de psychosociale oncologie is onmisbaar geweest voor mijn onderzoek. Daarnaast was je voor mij altijd laagdrempelig bereikbaar en dacht je mee graag over oplossingen. Je hebt er ook voor gezorgd dat ik binnen de afdeling medische psychologie kennis kon maken met andere onderzoekers. Dat bracht naast het delen van kennis ook de nodige gezelligheid met zich mee, zoals tijdens het etentje dat je organiseerde bij jouw thuis. Jouw enthousiasme bij het behalen van een mijlpaal, zoals de award voor beste poster op het jaarlijkse NVPO congres, maakte dat ik nog meer kon genieten van het behaalde resultaat. Heel veel dank.

Professor Van Herpen, beste Carla, ik ben je heel erg dankbaar voor jouw vertrouwen in mij. Wanneer zich een hobbel in de weg voordeed kon ik bij je terecht en sprak je dit vertrouwen ook uit. Jij maakte dat wat voor mij complex was, weer simpel. Dat heeft mij geholpen om deze hobbels te nemen en mijn weg weer te vervolgen. Ik waardeer jouw pragmatisme en kennis enorm en ik kijk altijd met veel bewondering naar jouw inzet voor patiënten en hun naasten. Jouw drive om hen de best mogelijke zorg te leveren, deel ik. Ik hoop dat wij deze energie in de toekomst nog vaak in iets constructiefs kunnen omzetten.

Doctor Wymenga, beste Machteld, ik kan mij nog goed herinneren dat ik jou voor het eerst leerde kennen als tutor tijdens mijn eerste co-schap bij de interne geneeskunde in Medisch Spectrum Twente. Je inspireerde mij door je gedrevenheid, duidelijkheid en hart voor de patiënt. Toen ik net begon als dokter, heb je mij "onder je vleugels genomen" en veel kansen voor mij gecreëerd, waaronder de mogelijkheid om dit promotietraject te starten. Ik zal het nooit vergeten en ik ben je heel dankbaar. Ondanks dat onze wegen zich "promotie-technisch" nu scheiden, hoop ik dat wij elkaar in de toekomst nog mogen vinden in de gedeelde passie die "palliatieve zorg" heet.

Prof. dr. Speckens, **prof. dr. Blijlevens** en **prof. dr. Van der Rijt**, heel veel dank voor het lezen en beoordelen van mijn manuscript en jullie deelname aan de oppositie tijdens de verdediging van mijn proefschrift.

Co-auteurs, jullie feedback op de inhoud van de verschillende hoofdstukken was erg waardevol waarvoor mijn dank. In het bijzonder wil ik een aantal mensen bedanken. **Marlies Peters**, het was fijn om met jou samen te mogen werken aan de fase I studie en jouw nuchtere woorden waren altijd weer een stimulans om verder te gaan. **Claudia van Opstal**, jouw drive voor patiënten met hoofdhalskanker en hun naasten werkte aanstekelijk en ik ben blij dat ik "jouw pilot" ook de mijne heb mogen maken. Veel dank daarvoor. **Marieke van de Wal**, met je doortastendheid en heldere kijk op de data hebben we een waardevolle paper kunnen schrijven over een belangrijk onderwerp. Bedankt voor de vlotte en prettige samenwerking. **Prof. dr. An Reyners**, bedankt voor je hulp bij het mede mogelijk maken van de studie naar mantelzorgers van patiënten met GIST en ook voor de waardevolle feedback op mijn paper. **Carel Veldhoven**, jouw pragmatische inborst als huisarts heeft mijn hoofdstuk over mantelzorgers van GIST patiënten een mooie draai gegeven. Veel dank voor je input en ik ben blij dat we kunnen blijven samenwerken binnen het Team Ondersteunende en Palliatieve Zorg.

Alle betrokken oncologen en verpleegkundigen in de deelnemende ziekenhuizen (Radboudumc te Nijmegen, Medisch Spectrum Twente te Enschede, Isala Klinieken te Zwolle, Slingeland Ziekenhuis te Doetinchem en het Universitair Medisch Centrum Groningen) wil ik heel hartelijk danken voor hun inzet voor de CoCare en GIVE studie. Ik wil hier in het bijzonder **Manon Hijmans-van der Vegte, Gerry Sieling**, **Chris Leverink** en **Brigitte Heck** bedanken voor hun inzet en fijne samenwerking.

Lieve medebewoners van de "Villa Interna Oude Stijl": **Chantal, Steve, Annelieke, Marye, Eline, Janneke, Marlies, Floor, Kalijn, Harm, Claudia, Daniëlle, Annemarie en Pieter**, veel dank voor de gezellige lunches, borrels en congresbezoeken. Ook de mijlpalen mocht ik met jullie vieren en dat was altijd een feest. In het bijzonder wil ik **Chantal** bedanken. Als kamergenoten heb we lief en leed gedeeld. Ik kijk nog steeds met een goed gevoel terug naar die tijd. Jij hebt mij geleerd dat ik het niet allemaal alleen hoef te doen en dat vragen altijd mag. **Steve**, ook met jou op de kamer kon ik altijd rekenen op gezelligheid. Ik heb altijd gelachen om jouw droge uitspraken, waarvan "Kun je rekenen? Reken er maar niet op!" toch echt mijn favoriet was. **Marlies**, jouw warme onthaal in Nijmegen heeft mij zacht doen landen en ik heb altijd genoten van onze mooie gesprekken. **Floor**, jouw luisterend oor en behulpzaamheid, ook bij de eindsprint voor mijn proefschrift, heb ik erg gewaardeerd. Je bent een topper. En ik wil hier ook even **Roos** noemen. Lieve Roos, ik beschouw het als een voorrecht dat ik je heb mogen leren kennen. Jouw warme persoonlijkheid en schaterlach zorgden er mede voor dat ik mij erg thuis heb gevoeld in de villa. Ook daarna heb ik met je mogen samenwerken als fellow bij de oncologie. Ik heb veel van je mogen leren. Dankjewel. Ik mis je.

Alle collega's van de afdeling medische oncologie, hartelijk dank voor de rol die jullie hebben gehad bij mijn onderzoek en de steun die ik heb mogen ervaren! De dames van het secretariaat, **Esther, Anja, Natasja en Sietske,** bedankt voor jullie ondersteuning bij praktische zaken, zoals het maken van afspraken met het promotieteam. Jullie zijn echte "puzzelpro's" wat mij betreft! Daarbij heb ik mij altijd welkom gevoeld en de persoonlijke gesprekken waren altijd gezellig. Ook alle verpleegkundige wil ik bedanken. Jullie oprechte interesse in mij en ook mijn onderzoek hebben mij altijd gesteund en jullie oog voor mantelzorgers is van grote waarde! In het bijzonder wil ik daarbij **Annemiek van Geffen** bedanken. Wij kennen elkaar al uit onze tijd in Medisch Spectrum Twente. Je bent een prachtmens en ik haal altijd veel uit onze gesprekken. Na jouw vertrek uit het Radboudumc hebben we contact gehouden en daar ben ik heel blij mee! De **fellows** waar ik mee heb mogen samenwerken toen ik de opleiding combineerde met het onderzoek. Veel dank voor jullie collegialiteit en steun! Ik ben blij dat ik die tijd met jullie heb mogen

samenwerken. **Rafke,** ik ben blij dat wij als collega's elkaar weten te vinden om samen te sparren. Dat is van grote waarde én natuurlijk ook gewoon gezellig. Ik wil mijn **opleiders en supervisoren** tijdens mijn opleidingstijd bij de oncologie bedanken voor hun geduld en steun. Het was prettig om van de besten te mogen leren. Bedankt. **Karin, your Ladyship, El Condor,** ik kon mij tijdens mijn stage op de afdeling geen betere supervisor wensen. Je liet me vrij en gaf mij veel vertrouwen. Het gaf de ruimte om soms ook te kunnen werken aan mijn onderzoek. Daarnaast hebben we veel kunnen lachen en zal ik nooit meer hetzelfde kunnen kijken naar Mr. Potato Head. Je werkt nu ergens anders, maar gelukkig zoeken we elkaar zo nu en dan toch nog wel eens op en dat vind ik onwijs leuk! Lieve **Ingrid,** je hebt mij als opleider altijd aangemoedigd om mijn eigen pad te gaan bewandelen en dat werpt nu zijn vruchten af. Ik kijk altijd met veel bewondering naar jouw vermogen om enkel uitdagingen te zien in plaats van problemen. Dat is een enorme inspiratie geweest en heeft mij ook geholpen om mijn promotietraject succesvol af te ronden. Heel veel dank.

Alle **collega's van de afdeling Pijn en Palliatieve zorg** en in het bijzonder **Kris, Heinrich, Evelien, Marieke, Carel, Hans, Henny, Floor, Nicole en Rina,** allen dank voor jullie steun! Beste **prof. dr. Kris Vissers**, wij delen een interesse voor de rol van de mantelzorger en ik ben je dankbaar voor de momenten dat ik hierover met je heb mogen sparren. Jouw oog voor de drukte tijdens de eindsprint van mijn proefschrift en hoe je mij daarbij uit de wind hebt gehouden, waardeer ik enorm. Nu volle kracht vooruit met mooie projecten in het verschiet! Lieve **Floor**, wat kan ik met je lachen en wat geniet ik daarvan! Lieve **Henny**, jouw oog voor naasten is onmisbaar in ons team en ik werk graag met je samen! Lieve **Heinrich**, naast een top collega ben je ook gewoon een heel fijn mens. Ik kijk uit naar meer dates samen met onze naasten, op een fijne plek en uiteraard met lekker eten en drinken! Lieve **Evelien**, tijdens mijn mammastage als fellow oncologie is onze samenwerking begonnen en dat hebben we mogen voortzetten tot op de dag van vandaag. Ik word daar blij van. Jij gaat altijd uit van het goede van de mens en maakt het ingewikkelde weer simpel. Zo heeft jouw slogan "dan promoveer ik toch gewoon een weekje later" de uitdagende momenten weer gerelativeerd. Lieve **Marieke, Eucalypta senior,** vanaf het moment dat wij mochten gaan samenwerken was er een klik. Het is top om met je te kunnen sparren en samen te lachen. Je hebt mij ook aangemoedigd om dit proefschrift af te ronden en tijd gecreëerd om hieraan te kunnen werken. Ik ben blij met jou als collega en ik hoop nog vele jaren met je samen te mogen werken! Lieve **Hans, Hanssie**, wat is het toch een voorrecht om jou als collega te mogen hebben. Jouw immer positieve kijk op de wereld werkt aanstekelijk. Bedankt voor je luisterend oor, de gezelligheid en "gewoon" voor het zijn van mijn maatje. Lieve **Maaike Haan**, ik ken jou via de afdeling **Pijn en Palliatieve zorg** door jouw onderzoek naar naasten

en jouw prachtige boek hierover. Onze gesprekken over dit onderwerp gaven mij elke keer weer nieuwe energie om verder te schrijven. Het bleek overigens al snel dat het gespreksonderwerp zich vaak niet beperkte tot praten over mantelzorgers. Wij praten de lunch zo vol over andere onderwerpen, zoals het moederschap en natuurlijk "de blauwe aap". Ik hoop dat we contact zullen houden!

Voor de mensen die mij gecoacht hebben, **Josefien, Nico en Mincka**: heel veel dank. Lieve **Josefien**, jij hebt mij zoveel helderheid gebracht. Wij hebben samen gewerkt aan mijn motto in het leven: "life isn't about waiting for the storm to pass, it's about learning to dance in the rain". Bedankt daarvoor! Beste **Nico**, bedankt voor het delen van jouw glasheldere kijk op succes! Het heeft mij geholpen om te komen waar ik nu sta. Lieve **Mincka**, jij hebt mij met veel humor en luchtigheid geleerd hoe fijn het is om de weg tussen het hoofd en het hart te onderhouden. Ik ben blij dat je op mijn pad gekomen bent!

Aan mijn lieve vrienden: heel veel dank voor jullie steun! Jullie maken mijn leven zoveel rijker en mooier. "As de moed oe in de kloompe zakt, dan mö'j 'n moal op oe'n kop goan stoan". Wijzen komen echt uit het Oosten. Lieve **Hilward, Marieke, Aafke, Ardo, Erwin, Dewi, Bianca, Jeroen, Leon, Linda, Nanda, Marloes, Ingrid, Hilde-Marie, Wilbert, Emile en Mireille**, jullie nuchtere kijk op de zaak geeft veel helderheid aan deze westerling. Ik ben heel blij dat ik jullie door Arjan heb mogen leren kennen! Lieve **Miranda**, naast jouw hulp thuis, beleef ik ook veel plezier aan onze gesprekken en de gezelligheid die dat brengt. Je bent een topper! Lieve **Cynthia**, ik zal nooit vergeten hoe jij mij gesteund hebt toen ik voor het eerst moeder werd. Jouw no-nonsense kijk op het leven is verfrissend en ik geniet van de gezelligheid tijdens een wandeling of etentje samen! Lieve **Bertine**, zonder dat je het misschien door hebt gehad, heb ook jij een belangrijke bijdrage geleverd aan het af komen van dit boekje. Na onze gezellige sportmomenten samen ging ik altijd weer met veel focus en energie aan het werk! Bedankt! Lieve **Elsemieke**, wij kennen elkaar nog niet lang, maar tijdens de eindsprint van mijn proefschrift was jij daar met een een goede bak Maastrichtse thee of gewoon een Brownie per post. Op naar meer mooie wandelingen, zanglessen en genieten met onze kindjes samen! Lieve dames van **Saffier**, de afronding van dit proefschrift zal er wat mij betreft zeker aan bijdragen dat we elkaar weer vaker kunnen zien. Ik kijk ernaar uit, want uit het oog is zeker niet uit het hart! Lieve **Lotgenoten**, **Middel, Baussie, Carin en Sonja**, wat is het toch mooi dat wij elkaar tijdens de co-schappen hebben gevonden en elkaar niet meer hebben losgelaten. We kunnen samen lachen, huilen en huilen van het lachen. Hoe "fijn" en "zalig" is dat!? Ik ben super blij met jullie in mij leven! Lieve **Nyn, Makkjèr,** wat is het toch een feest om jouw in mij leven te hebben! Jouw

steun, liefde, humor en energie zijn voor mij echt onmisbaar! Ik heb veel respect hoe jij jouw veerkracht elke keer weer toont. Nu er meer tijd komt zeg ik: op naar heel veel mooie, hysterische, play-back, "framboise" en fabulous momenten samen! Ik hou van je, toen, nu en voor altijd. Lieve **Té**, wij moeten jou missen, maar ik weet dat je met mij meekijkt, waar je ook bent. Jij zou ontzettend trots zijn geweest op wat ik voor elkaar heb gekregen. Ik zal nooit vergeten wat je zei als mantelzorger van **Gerrit:** "maar wie vraagt mij nou eigenlijk hoe het met mij gaat?". Dat heeft mij geïnspireerd om dit onderzoek te doen. Je bent voor mij een voorbeeld geweest als mens en als moeder van **Nyn**. Ik mis je. Lieve **Gerrit**, ik heb bewondering voor jou, voor hoe je in het leven staat en je door niks en niemand van jouw pad af laat brengen. Jij bent zo blij met de kleinste dingen. Bedankt voor onze herinneringen samen. Van "stop, ik moet dit doen" tot de BBQ's in de tuin in Leek samen met **Nyn** en **Té**; alle geven mij een grote glimlach op mijn gezicht.

Lieve **Martine** en **Hanneke**, wat ben ik trots dat jullie naast mij staan als paranimf. Jullie hebben een heel belangrijke rol gespeeld in alle fasen die ik heb doorlopen om dit proefschrift af te ronden. Lieve **Martine**, wat prijs ik mij gelukkig met een vriendin zoals jij. Jij bent mijn spiegel en geweten. En waar ik normaal "een mens van veel woorden" ben, heb ik er bij jou niet veel nodig om mij begrepen te voelen. Onze onvoorwaardelijke vriendschap is van de buitencategorie. Om samen met jou door het leven te mogen navigeren, wat wij al mogen doen vanaf 3 VWO, zie ik als een groot cadeau. Bedankt voor jouw onvoorwaardelijke steun. Lieve **Hanneke**, vanaf het moment dat wij elkaar hebben leren kennen tijdens de introductie cursus van de RIHS zijn we niet meer gestopt met praten. Jouw gedrevenheid en doortastendheid zijn inspirerend voor mij geweest en ik word altijd weer blij van jouw scherpe geest en goede gevoel voor humor. Op de Wolfsberg, bij Beluga, Krentemans of lekker thuis; onder het genot van een goed glas wijn en lekker eten praten we samen over "het leven". Dat we dit in alle eerlijkheid kunnen doen is zo fijn. Wat bof ik toch met jou als vriendin. Ik vind je echt een prachtmens!

Aan mijn familie die mij hebben gesteund tijdens mijn promotietraject: heel veel dank! Lieve **Stan**, onze aankomst in het mooie Zutphen in 2013 was er dankzij jou één met een gouden randje. Jij hebt ons wegwijs gemaakt en laten zien wat Zutphen allemaal te bieden heeft. Ik geniet van jouw positieve inborst en verhalen over vroeger. Ik hoop nog vele kopjes koffie of borrels (bij voorkeur op de Bokbierdag) met je te mogen drinken. Lieve **Roos** en **Tom**, van een goed glas wijn in de sneeuw in Méribel, een onvergetelijke rit in de Alvis op onze bruiloft tot gewoon dat een appje op de verjaardagen; ik geniet van het contact dat er is. Lieve **Ilona** en **Ruud,** ik heb fijne herinneringen aan het logeren bij jullie vroeger en ik vind

het leuk om samen herinneringen op te halen, ook aan **opa** en **oma Langenberg**. Ik mag ook nog graag in het fotoboek kijken wat jullie hebben gegeven. Jullie interesse in mij en mijn gezin waardeer ik ontzettend. Bedankt! Lieve **Peter**, wat hebben wij een fijne traditie in het voorjaar in het mooie Schönried! Ook de borrels samen en de kaasfondue zijn altijd weer een feest! Maar bovenal jouw interesse in wat ik doe en wat mij bezighoudt ben ik je dankbaar voor. Ik hoop nog lang van je te mogen genieten en samen de fijne herinneringen aan opa **Siem** en oma **Door Nadorp** levendig te mogen houden! Lieve **Dick,** in onze gesprekken "als collega's onder elkaar" kwam ik tot de ontdekking dat wij een interesse delen: het welzijn van mantelzorgers. Jij hebt als huisarts hier een belangrijk bijdrage geleverd in de regio rondom Bemmel. Ook spreek ik soms patiënten of collega's die jou nog hebben gekend als huisarts. De mooie woorden die volgen maken mij trots en motiveren mij om mij als dokter volledig in te blijven zetten voor de mens achter de patiënt. Je geniet samen met **Ria** van het leven. Jullie zijn een ijzersterk duo en dat vind ik mooi om te zien. Lieve **Door en Frans,** jullie wonen dicht in de buurt en vanaf dat ik een klein meisje ben kom ik graag bij jullie. Met het afronden van dit proefschrift hoop ik dat ik vaker richting het Lochemse kan komen! Lieve **Jos**, met trots kan ik zeggen dat ik in jouw voetsporen ben getreden als internist. En dat niet alleen. In 1974 mocht ook jij in Nijmegen jouw proefschrift verdedigen. Je was dan ook blij verrast te horen over mijn voornemen datzelfde te gaan doen. Helaas kunnen we deze mijlpaal niet meer samen vieren, maar ik weet zeker dat jij heel trots op mij zou zijn geweest. Lieve **Tineke,** ik bewonder jou om de vrouw die je bent: sterk, doortastend, warm en oprecht. Ook na het overlijden van Jos toon jij jouw kracht. Daar heb ik veel respect voor.

Lieve **Rogier**, jij brengt altijd reuring en gezelligheid met je mee. Daar kan ik echt van genieten en dat heeft zeker bijdragen aan de ontspanning die nodig was om elke keer weer met nieuwe energie aan het werk te gaan om dit traject af te ronden. Bedankt! Lieve **Monique,** ik vind je een onwijs mooi mens en ik bewonder jouw geduld en veerkracht echt. Het is een geluk om jouw als schoonzus te mogen hebben. Lieve **Pien**, ik kan mij het moment dat wij voor het eerst kennis maakten nog goed herinneren. Je was zo mooi en dat ben je nog steeds, in alle opzichten. Jou op te mogen zien groeien tot de mooie dame die jij bent, vind ik zo bijzonder leuk. Lieve **Jonas**, jij bent er één uit duizenden. Zo lief en in het bezit van een goede dosis humor. Ik kan daar met een grote glimlach en veel trots naar kijken! Lieve **Henk** en **Gera**, dit proefschrift was nog lang niet af geweest als jullie er niet geweest waren. Ik waardeer jullie steun en liefde ontzettend. Het denken in oplossingen, zoals jullie dat als de besten kunnen, hebben mij enorm geholpen. Ik geniet ervan om te zien hoe mooi jullie band is met Hugo en Milou en ik hoop daar nog lang

(en nu het proefschrift af is nog meer) van te mogen genieten. Op naar nog meer fijne momenten samen; thuis, op Texel of in de sneeuw! Lieve **Oma Oma,** vanaf het eerste moment dat je mij zag, heb je mij omarmt en niet meer losgelaten. Het was zo'n warm welkom in jullie familie. Tijdens de start van mijn promotietraject heb je bijgedragen aan de nodige ontspanning en mochten we regelmatig bij je aanschuiven voor pannenkoeken of een heerlijke jachtschotel. Ik had deze mijlpaal dan ook graag met je gevierd. Als ik het glas hef om te proosten op de afsluiting van dit traject, zal ik zeker aan je denken!

Lieve **Francis**, wij hebben een speciale band en daar ben ik elke keer weer blij mee. Wij lijken op elkaar en toch ook weer niet. Je bent voor mij altijd een inspiratie geweest om recht op je doel af te gaan en daar ook veel voor over te hebben. Wat ik altijd fijn heb gevonden en wat nog altijd zo is, is de wetenschap dat jij er voor me zal zijn als ik je nodig heb. Bedankt voor wie je bent en wie je voor mij bent. Ik hou van je. Lieve **Sanne**, wat ben ik blij dat jij in onze familie bent gekomen. Jouw nuchtere kijk op zaken heeft mij echt geholpen. Ik ben blij dat wij "de liefde voor het genieten van het leven" mogen delen. Ik hoop dat dan ook nog vaak samen te mogen doen. Natuurlijk ben ik ook zo blij met jullie mooie kindjes **Just** en **Jo**. Lieve **Just**, jouw nieuwsgierigheid en prettige eigenwijsheid toveren elke keer weer een lach op mijn gezicht. Lieve **Jo**, die ondeugende blik in jouw ogen en de gekke bekken die je trekken kan, maken mij altijd vrolijk. Jullie hebben een speciaal plekje in mijn hart. Lieve **papa**, ik voel mij altijd gesterkt, wetende hoe trots je op mij bent. Bedankt voor jouw geloof in mij. Het was onmisbaar en dat heeft mij echt gesteund tijdens mijn promotietraject. Ik kan met bewondering kijken naar hoe jij je met veel daadkracht en energie inzet voor iets waar jij in gelooft en waar jij om geeft. Daar mag ook ik de vruchten van plukken! Ik hou van jou en ik hoop dat er nu tijd komt om eens samen af te reizen naar Wenen! Lieve **mama**, bedankt voor wie je bent, voor wat je mij geleerd hebt, voor je oneindige liefde, geduld, interesse en steun. Zonder jou had ik dit zeker weten niet tot zo'n mooi einde weten te brengen. Jouw zorgen voor anderen en de liefde en energie die je aan anderen geeft (en je soms ook iets teveel kosten), zijn een inspiratie geweest om dit onderzoek te willen doen. Ik hoop dat met de tijd die vrij komt na het afronden van dit werk, er meer tijd komt om samen te genieten zoals wij dat samen kunnen…Ik hou van jou.

Lieve **Hugo** en **Milou**, dat jullie in mijn leven gekomen zijn, is echt een impuls geweest om dit proefschrift af te willen ronden. Alle tijd die ik met jullie mag doorbrengen is namelijk één groot cadeau. Om de gezelligheid, maar ook om de lessen die ik leren mag. Elke dag weer kijk ik met zoveel bewondering naar jullie. Jullie leren mij waar het echt om draait in het leven. Lieve **Hugo**, je bent zo wijs,

sterk en oprecht en ik bewonder je daarom enorm. Met een grote lach op je gezicht geniet jij van het leven, omarm je iedereen op jouw pad en mag ik er getuige van zijn hoe jij met grote nieuwsgierigheid de wereld ontdekt. Wat een feest! Lieve **Milou**, wanneer jij met een twinkeling in je ogen voor mij "laat het los, laat het gaan" zingt en daarbij jouw mooiste dans danst, raak je mij en weet ik waar ik het allemaal voor doe. Jij bent zo'n onwijs lieve mantelzorger voor je knuffels en poppen en ik geniet ervan dat te mogen aanschouwen. De wetenschap dat ik nu meer tijd overhoud om samen met jullie op avontuur te gaan, maakt mij heel gelukkig! Ik hou van jullie! Lieve **Arjan**, makker, jouw steun in alle fasen van mijn promotietraject zijn van ongekende waarde geweest. Zoals je zelf altijd zo mooi zegt: "luctor et emergo". Ik worstel en kom boven. Dat lukt ook elke keer weer, wetende dat jij daar staat, met open armen en de beste omhelzing die ik me maar kan wensen. In alle opzichten, zowel praktisch als emotioneel, wist je mij te steunen. Niks was jou teveel. Jij bent voor mij zo'n bijzonder, mooi en uniek mens. Jij herinnert mij er elke keer weer aan dat ik er mag zijn, gewoon zoals ik ben. Het is een voorrecht om met jou samen te mogen zijn en ik geniet van onze momenten met elkaar, groot en klein. Ik hou van jou, je bent mijn alles(sie)! Nu dit avontuur tot een einde komt, staat ons samen een nieuwe te wachten: ons droomhuis vormgeven op een droomplek. Ik kan niet wachten!

Appendix

Curriculum Vitae

CURRICULUM VITAE

Simône Langenberg werd op 30 september 1984 geboren in Loosdrecht, waar zij ook opgroeide. In 2002 behaalde zij haar VWO diploma aan het Alberdingk Thijm College in Hilversum. In 2002 begon zij aan haar opleiding Geneeskunde aan de Rijksuniversiteit Groningen. Voor haar wetenschappelijke stage deed zij onderzoek met als onderwerp "in vivo validatie van de colon delivery capsule" (supervisor dr. F. Stellaard, Universitair Medisch Centrum Groningen). Op 9 april 2009 studeerde zij af als basisarts en is zij, na een talencursus Frans in Montpellier (juni 2009), op 1 augustus 2009 begonnen aan haar opleiding tot internist (Universitair Medisch Centrum Groningen). De eerste drie jaar van de opleiding heeft zij volbracht in Medisch Spectrum Twente te Enschede (opleider W.M. Smit). In 2013 heeft zij haar opleiding tot internist voor 2 jaar onderbroken voor haar promotie traject op de afdeling Medische Oncologie van het Radboudumc te Nijmegen. Onder begeleiding van prof. dr. W.T.A. van der Graaf, prof. dr. J.B. Prins, prof. dr. C.M.L. van Herpen en dr. A.N.M. Wymenga deed zij onderzoek naar naasten van patiënten met kanker. In februari 2015 hervatte zij haar opleiding tot internist en begon zij in december 2015 aan haar subspecialisatie tot internist-oncoloog. Zij heeft op 14 februari 2019 haar opleiding afgerond (hoofdopleiders interne geneeskunde prof. dr. J. de Graaf & dr. G.M.M. Vervoort; hoofdopleiders differentiatie oncologie prof. dr. ir. J.J.M van der Hoeven & dr. I.M.E. Desar). Tijdens haar differentiatie tot internist-oncoloog heeft zij in het kader van een keuze stage gedurende 6 maanden gewerkt in het team Ondersteunende en Palliatieve zorg op de afdeling Anesthesiologie, Pijn & Palliatieve zorg van het Radboudumc. Zij is sinds het afronden van haar opleiding binnen ditzelfde team werkzaam als internist-oncoloog.

Simône is getrouwd met Arjan de Mare waarmee zij haar zoon Hugo (2016) en dochter Milou (2018) heeft gekregen. Zij wonen samen in Zutphen.